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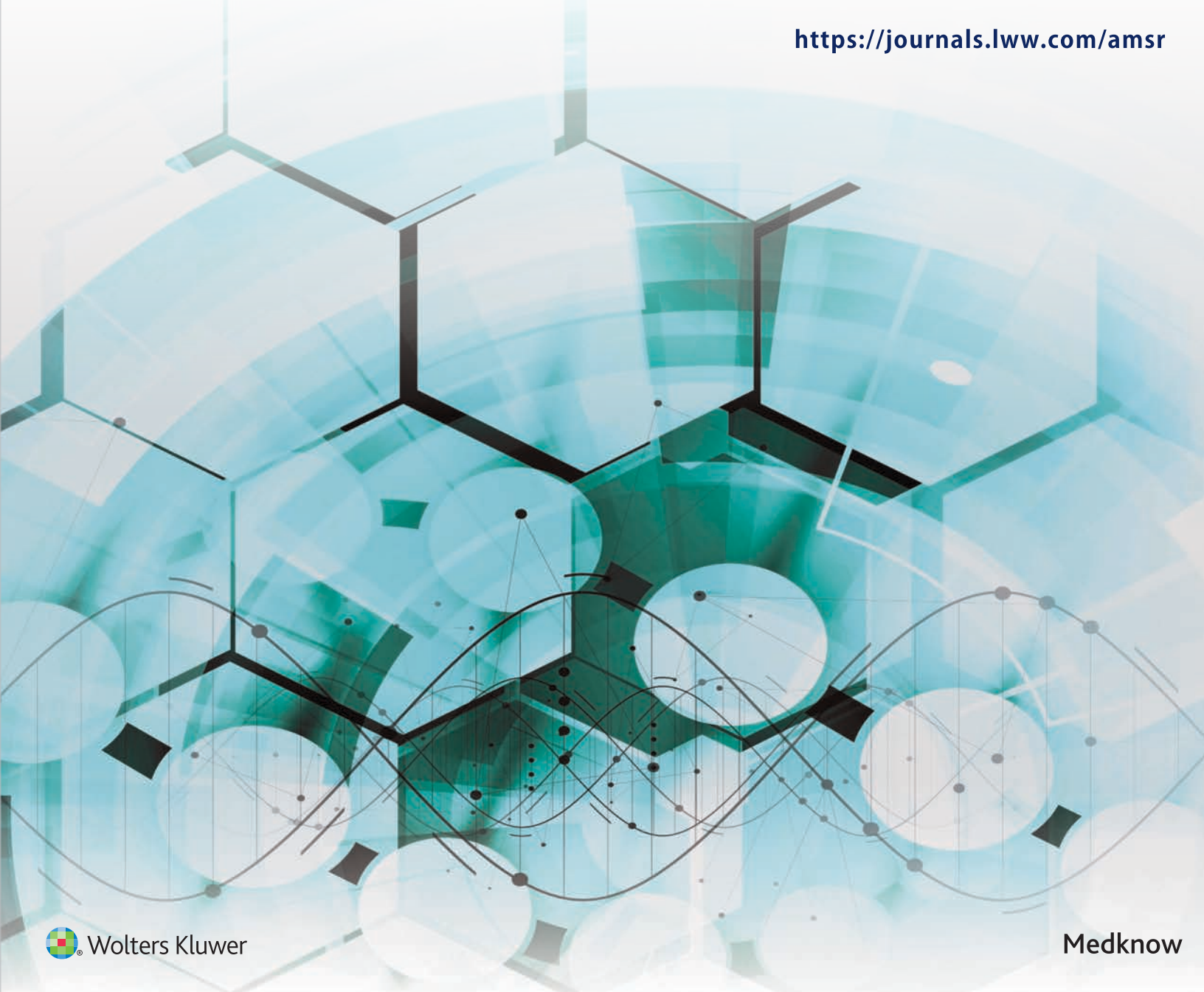

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The evidence for evidence-based medicine

INTRODUCTION

"Seeing is believing," "the proof of the pudding is in the eating," and so many such phrases echo similar sentiments that we can trust what we see, feel, and experience. This applies to all aspects of human understanding and more so to scientific knowledge. We believe, accept, apply, and perpetuate information backed with proof and rigorously generated data; the so-called evidence-based medicine (EBM). EBM, therefore, is the judicious and reasonable use of knowledge of modern medicine for adopting the management strategy that will benefit our patients. Research is an ongoing phenomenon, and what is updated today will soon become outdated. The physician is therefore required to update himself on a daily, or rather real-time basis. Close to 2 million articles are published each year in various medical journals, and a number greater than this are rejected.[1] Therefore, a doctor must select what to read and make the best utilization of his available time.[2]

HISTORY

EBM is stated to date back to the 11th century when the Persian physician and philosopher Avicenna developed a concept of EBM that was similar to what we understand today.[3] However, it may have been a military leader, Nebuchadnezzar, who ruled over Babylon for 60 years around 500BC, who conducted something like the first clinical trial to decide whether some of his subjects could continue on a vegetarian diet according to their choice. John Baptist Van Helmont first described the concept of controlled clinical trials in 1962, referring to the practice of bloodletting. The US FDA's Kefauver Harris Act of 1962, which came after the Thalidomide tragedy (in which thousands of children were born with birth defects as a result of their mothers taking thalidomide for morning sickness during pregnancy), introduced a requirement for drug manufacturers to provide proof of the effectiveness and safety of their drugs before approval. The *term* EBM was coined by Gordon Guyat only in 1990 at the University of McMaster[4] and published as an editorial in the Annals of Internal Medicine in 1991.

THE NEED FOR EVIDENCE-BASED MEDICINE

Clinical decision-making is what the physician faces every day. This is more applicable to the primary care physician who has to make treatment decisions without the backup of detailed and high-end diagnostic support. For example, how is the attending doctor to decide whether to start antibiotics in a patient with fever when the fever does not abate after 48–72 h? Once he decides to use an antibiotic, he then has to face the task of choosing which antibiotic to use. Let's take another example where the doctor is faced with the dilemma of ordering a CT scan for a patient with a headache. Many of these decisions are based on experience and apprehension of litigation, and the physician generally errs in favor of committing rather than omitting. EBM can be a useful rescue in such situations and provide data-based information which can help us best treat the patient and avoid medico-legal hassles. The need for EBM was further felt after the promotion of prophylactic Class I antiarrhythmic therapy in patients with myocardial infarction in the 1980s and early 1990s, based on physiological reasoning that suppression of arrhythmias would reduce mortality, proved disastrous—more Americans died from the use of these drugs than in the Vietnam War!

LEVELS OF EVIDENCE

Once we have decided to base our practice on EBM, the next question is the quality of evidence or the level of evidence. EBM grades clinical evidence according to their quality. Randomized, placebo-controlled, well-blinded clinical trials provide the highest quality of evidence, whereas case reports and case series provide low-quality evidence.[5]

A system of grading evidence commonly adopted by clinicians was proposed by the USPSTF in 1989[6]

1. Level I: Evidence obtained from at least one properly designed randomized controlled trial (RCT).
2. Level II
   - Evidence obtained from well-designed nonrandomized controlled trials.
   - Evidence obtained from well-designed cohort studies or case-control studies, preferably from more than one center or research group.

   - Evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
3. Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

LIMITATIONS AND CRITICISM OF GUIDELINES BASED ON RANDOMIZED CONTROLLED TRIAL

RCT promises to provide solutions to our clinical dilemmas, but it is not the holy grail of clinical medicine.[7] Let us try and understand the limitations of RCTs:

Nongeneralisability of results

All clinical trials have strict inclusion and exclusion criteria; as a general statement, it is true that the elderly and women are often under-represented. This is particularly relevant in a condition like myocardial infarction, where the elderly (>75 years of age) constitute 37%, but they are represented in clinical trials only to the extent of 9%. The data from RCT may not be applicable to the whole or part of the population.[8] Hence, the importance of real-world evidence studies as well.

Lag time

There is a lag time between conducting research and generating the results. Similarly, there is a lag time between research and its application in clinical practice. Excess delays in data generation may make research outdated and irrelevant by the time it is available for clinical use[9]; this may be relevant to COVID-19.

Cost

Research, especially high-quality research like RCT, is expensive and may, therefore, be a monopoly of only the "giants" in the pharmaceutical industry; such costs will naturally add to the price of the medicine that the patient has to buy.

Unbiased bias

EBM promises to be unbiased, but there are a number of steps where bias may creep into the so-called foolproof research methodology. Inclusion criteria, exclusion criteria, choice of outcomes, analysis methods, and statistical tools applied can be selected at the discretion of the investigator and influence results and the evidence generated.[10,11]

Corporate and industry pressure

The cost involved in research makes funding pivotal, and here comes the role of funding agencies. Industry-driven research is influenced by the sponsors, and the research methodology can be modified to suit the interests of corporate funding agencies. Numerous such examples exist, particularly in the cardio-diabetes pharma-driven trials where similar trials have generated conflicting results, confusing the clinician.[12]

Statistical versus clinical significance

One needs to understand that there is nothing magical or sacrosanct about data showing $P < 0.05$, a commonly used cutoff for statistical significance.

Many a time, the relative risk reduction seems quite large, while absolute risk reduction is minuscule; the former may be stressed upon by the pharmaceutical industry. It is also important to realize that none of the "positive" clinical trials have a number needed to treat (NNT) (to show benefit) of 1. One should try to look for the NNT in such clinical trials; if it is x and the duration of the trial is y years, it means that x number of individuals need to be treated for the period of y years in order to demonstrate reduction of one clinical event. Hence it is important for the treating clinician to understand that the purported benefits demonstrated in an RCT may not accrue to every patient the drug is prescribed for.

The bias of the easily measurable

One needs to realize that ill-health is not a binary phenomenon (presence or absence); moreover, objective data often fails to capture less tangible (nonetheless important) issues like quality of care or patients' experience.

Choice of comparator

It is well-accepted and recommended to use a placebo in many RCTs, though it may be more ethical to use an "active" comparator.

"Evidence" for evidence-based medicine

It would have been ideal to demonstrate the efficacy of the concept of EBM over "experience-based medicine"; intuitively, it seems that EBM would be better, but I am not aware of such evidence being available.

THE WAY FORWARD

For EBM to provide true benefit, it should not be corrupted by corporate interests, academia should not be commercialized, there should be appropriate regulations, and these should be rigorously implemented. Finally, there should be a "reliable" second-order peer review of published articles, which can then be filtered down so that the busy clinician needs to read only up to 20 new articles per year.[13] At this point in time, it appears that in the

not-so-distant future artificial intelligence may help in the clinicians' decision-making process.

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Review Article

Treatment with oral or inhaled bronchodilator without inhaled corticosteroids in bronchial asthma: A dangerous weapon!

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Abstract

Bronchial asthma is the most common chronic lung disease in the obstructive airway disease category with the characteristic feature of "reversible" airflow obstruction. Despite an increase in awareness of risk factors, diagnosis, and treatment options available to treat bronchial asthma, more than half of cases received irrational treatment. Inadequate treatment is reasoning more morbidity and mortality of this easily treatable disease. Inhaled short- and long-acting bronchodilators, antimuscarinic agents, and inhaled corticosteroids (ICSs) are the cornerstone of the treatment of asthma and are categorized as "rescue and controller" role in disease management. Bronchodilators without ICSs are not recommended because of more harm than benefit in bronchial asthma. ICSs are the gold standard and the recommended treatment for asthma due to their anti-inflammatory and disease-modifying property labeled as "game changer role." Bronchodilators with ICSs will have added benefit of symptom control, improvement in quality of life, and decrease in exacerbation. Combo of bronchodilators with ICSs will decrease the overall cost of care in asthma by improving disease control and decrease in emergency room visits and hospitalizations in intensive care units due to exacerbations.

Keywords: Airflow obstruction, bronchial asthma, bronchodilator, inhaled corticosteroids

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INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitation.[1] The prevalence of bronchial asthma differs globally due to diverse geographical, dietary, environmental, and cultural trends. The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults estimated the national burden of asthma at 17.23 million with an overall prevalence of 2.05%.[2] The studies showed that around 6% of children in India had current wheezing and identified several environmental factors associated with asthma globally, including environmental tobacco smoke, cooking with firewood, exposure to heavy

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truck traffic, obesity, fast-food consumption, dampness in homes, and paracetamol/antibiotic use.[3,4] India now contributes to an alarming 42.4% of all global asthma deaths, although it accounts for only 12.9% of global asthma cases. Moreover, India ranks number one in the world for disability-adjusted life years due to asthma (5.83 million), four times above China (1.41 million), which ranks second.[5]

Pathophysiology of asthma and phenotypes

Bronchial asthma afflicts about 10% of children and 5% of adults. Childhood asthma is usually due to allergies. In 30%–50% of asthmatic adults, no allergy is found as the cause of asthma. Airway obstruction in bronchial asthma is mainly caused by contraction of bronchial smooth muscle, edema of the airway wall, mucous plugging of the bronchioles, and irreversible changes in the lungs called "remodeling."[6]

Asthma is associated with T helper cell type-2 (Th2) immune responses, which are typical of other atopic conditions. Elevated levels of Th2 cells in the airways release specific cytokines, including interleukin (IL)-4, IL-5, IL-9, and IL-13, and promote eosinophilic inflammation and immunoglobulin E (IgE) production.[7] Over time, the airway remodeling that occurs with frequent asthma exacerbations leads to greater lung function decline and more severe airway obstruction. This highlights the importance of frequent assessment of asthma control and the prevention of exacerbations.[8] The characterization of this heterogeneity has led to the concept that asthma consists of various "phenotypes" or consistent groupings of characteristics.[9] In children with asthma, three wheezing phenotypes have been identified: (1) transient early wheezing; (2) nonatopic wheezing; and (3) IgE-mediated (atopic) wheezing.[10]

Clinical and immunological phenotypes were categorized as T2-high and non-T2-high groups. The T2-high asthma endotype encompasses several related subtypes in both children and adults. T2-high phenotypes have been classified into three groups: early-onset allergic asthma, late-onset eosinophilic asthma, and aspirin-exacerbated respiratory disease.[11] Eosinophilic airway inflammation is one of the most influential traits in asthma and accounts for approximately 40%–60% of patients with severe asthma. The analysis of eosinophils in induced sputum is a common technique to characterize T2 asthma. Sputum eosinophils are considered the "gold standard" type 2 biomarker with cutoff points of more than 3%.[12]

T2-low or non-T2 phenotypes have been classified according to clinical characteristics that include obesity, smoking, and age. T2-biased airway inflammation is observed in only half of the patients with asthma and only in 37% of patients with severe asthma from airway epithelial transcriptome analysis.[13,14] It is generally characterized by neutrophilic (sputum neutrophils > 40%–60%) or paucigranulocytic (normal sputum levels of both eosinophils and neutrophils) inflammation and a lack of response to corticosteroid therapy. The mechanisms underlying the recruitment and maintenance of neutrophilic airway inflammation are yet unknown. Severe neutrophilic asthma has been associated with chronic infection with atypical bacteria, obesity, smoking, and poorly understood underlying smooth muscle abnormalities.[14] Neutrophilic inflammation cannot be detected based on currently available biomarkers. IL-6 is a pleiotropic cytokine produced by various cell types in response to a wide range of inflammatory stimuli. It is considered an indicator of metabolic dysfunction as well as asthma severity and has been identified as a potential candidate biomarker in a study with obese asthmatic patients.[15]

There are limited data about the natural history of asthma after diagnosis, but one longitudinal study showed that approximately 16% of adults with recently diagnosed asthma may experience clinical remission (no symptoms or asthma medication for at least 1 year) within 5 years.[16]

Diagnosis of asthma

The diagnosis of asthma is based on the history of characteristic symptom patterns and evidence of variable expiratory airflow limitation. This should be documented from bronchodilator reversibility testing or other tests.[1] This is important to avoid unnecessary treatment or over-treatment, and to avoid missing other important diagnoses. The diagnosis of asthma was less likely to be confirmed in patients who had no lung function testing performed at the time of initial diagnosis. Some patients (2%) had serious cardiorespiratory conditions that had been misdiagnosed as asthma.[17]

Lung function testing should be carried out by well-trained operators with well-maintained and regularly calibrated equipment, with an inline filter to protect against transmission of infection. Forced expiratory volume in 1 s (FEV1) from spirometry is more reliable than peak expiratory flow (PEF). If PEF is used, the same meter should be used each time, as measurements may differ from meter to meter by up to 20%.[18] "Variability" refers to improvement and/or deterioration in symptoms and lung function. Excessive variability may be identified over 1 day (diurnal variability), from day to day, from visit to visit, or seasonally, or from a reversibility test. "Reversibility"

(now called "responsiveness") generally refers to rapid improvements in FEV1 (or PEF), measured within minutes after inhalation of a rapid-acting bronchodilator such as 200–400 mcg salbutamol, or more sustained improvement over days or weeks after the introduction of effective controller treatment such as inhaled corticosteroids (ICSs).[19] Generally, in adults with respiratory symptoms typical of asthma, an increase or decrease in FEV1 of more than 12% and more than 200 mL from baseline, or (if spirometry is not available) a change in PEF of at least 20%, is accepted as being consistent with asthma.

One option for documenting variable expiratory airflow limitation is to refer the patient for bronchial provocation testing to assess airway hyperresponsiveness. Challenge agents include inhaled methacholine, histamine, exercise, eucapnic voluntary hyperventilation, or inhaled mannitol. These tests are moderately sensitive for a diagnosis of asthma but have limited specificity. For example, airway hyperresponsiveness to inhaled methacholine has been described in patients with allergic rhinitis, cystic fibrosis, bronchopulmonary dysplasia, and chronic obstructive pulmonary disease (COPD). This means that a negative test in a patient not taking ICS can help to exclude asthma, but a positive test does not always mean that a patient has asthma.[20]

Atopic status can be identified by skin prick testing or by measuring the level of specific IgE (sIgE) in serum. Skin prick testing with common environmental allergens is simple and rapid to perform and, when performed by an experienced tester with standardized extracts, is inexpensive and has a high sensitivity. Measurement of sIgE is no more reliable than skin tests and is more expensive. sIgE analysis may be preferred in cases with widespread skin disease, in uncooperative patients and in settings where history suggests a risk of anaphylaxis with skin test.[21]

The fractional concentration of exhaled nitric oxide (FeNO) is modestly associated with levels of sputum and blood eosinophils. FeNO is higher in asthma that is characterized by type 2 airway inflammation. Importantly, it is also elevated in nonasthma conditions such as eosinophilic bronchitis, atopy, allergic rhinitis, and eczema. Surprisingly, it is not elevated in some asthma phenotypes such as neutrophilic asthma. FeNO is lower in smokers, and during bronchoconstriction and the early phases of allergic response; it may be increased or decreased during viral respiratory infections.[22]

Treatment recommendations in asthma

The goals of pharmacotherapy are the suppression of the inflammation of asthma and the reduction of bronchial hyperreactivity and airway obstruction. Controller medications are a group of medications that contains ICS and are used to reduce airway inflammation, control symptoms, and reduce future risks such as exacerbations and related decline in lung function. Reliever medications are provided to all patients for as-needed relief of breakthrough symptoms, including during worsening asthma or exacerbations. Relievers are divided into as-needed low-dose ICS-formoterol (the preferred reliever, but not if the maintenance controller contains a different ICS-long-acting beta-agonist) or as-needed SABA. Overuse of short-acting beta-agonists (SABA) (e.g., dispensing of three or more 200-dose canisters in a year, corresponding to average use more than daily) increases the risk of asthma exacerbations. Reducing and, ideally, eliminating the need for SABA reliever are both an important goal in asthma management and a measure of the success of asthma treatment. Formoterol can be used as a reliever because of its rapid onset of action or as a controller in combination with corticosteroids.[23]

In clinical practice, the choice of medication, device, and dose for controller and reliever should be based on each patient on assessment of symptom control, risk factors, patient preference, and practical issues (cost, ability to use the device, and adherence). Once good symptom control has been maintained for 2–3 months, the ICS dose should be carefully titrated to the minimum dose that will maintain good symptom control and minimize exacerbation risk, while reducing the potential for side effects.

Do bronchodilators without ICS are useful in asthma? or it is worsening asthma?

Beta2-agonists are thought to cause bronchodilation primarily through binding beta2-adrenoceptors on airways smooth muscle, with subsequent activation of both membrane-bound potassium channels and a signaling cascade involving enzyme activation and changes in intracellular calcium levels following a rise in cyclic adenosine monophosphate. However, beta2-adrenoceptors are also expressed in a wide range of cell types where beta2-agonists may have a clinically significant effect including airway epithelium, mast cells, postcapillary venules, sensory and cholinergic nerves, and dendritic cells. Beta2-agonists will also cross-react to some extent with other beta-adrenoceptors including beta1-adrenoceptors in the heart.[24] Drugs that fully activate a receptor are known as full agonists and those that partially activate a receptor are known as partial agonists. Efficacy also is very much dependent on the system in which it is being tested and is affected by factors including the number of receptors available and the presence of other agonists and antagonists. Thus, while salmeterol acts as a partial agonist

in vitro, it causes a similar degree of bronchodilation to the strong agonist formoterol in stable asthmatic patients.[25]

This hypothesis states that the direct adverse effects of beta2-agonists are responsible for an associated increase in mortality, and most research in the area has concentrated on effects detrimental to the heart. While it is often assumed that cardiac side effects of beta2-agonists are due to cross-reactivity with beta1-adrenoceptors (i.e., poor selectivity), it is worth noting that human myocardium also contains an abundance of beta2-adrenoceptors capable of triggering a positive chronotropic and inotropic response. Generalized beta2-adrenoceptor activation can also cause hypokalemia, and it has been proposed that, through these and other actions, beta2-agonists may predispose to life-threatening dysrhythmias or may cause other adverse cardiac effects.[26,27] When increasing actuations of standard doses of formoterol and salmeterol inhalers are compared in stable asthmatic patients, relatively similar cardiovascular effects are seen at lower doses. However, at the highest doses (above those recommended by the manufacturers), there were trends toward an increase in systolic blood pressure with formoterol; in comparison, there was a trend toward a decrease in diastolic blood pressure and an increase in corrected QT interval with salmeterol.[28]

Toxicity or adverse events associated with beta-agonist use in asthma

Confounding by severity

Historically, this hypothesis has been used extensively to try to explain the association between mortality and the use of fenoterol during the 1970s New Zealand epidemic, and it is still quoted today. The hypothesis essentially relies on the supposition that patients with more severe asthma are more likely to take either higher doses of beta2-agonists or a particular beta2-agonist (such as fenoterol), thereby explaining the association.[29]

The delay hypothesis

This hypothesis accepts that beta2-agonists or a particular beta2-agonist can cause an increased risk of mortality, but indirectly by causing patients to delay before getting medical help and further treatments including high-dose steroids and oxygen. There is evidence that both salmeterol and formoterol can reduce awareness of worsening underlying inflammation. It is difficult to rule out the delay hypothesis in explaining or contributing toward both asthma mortality epidemics and an association with regular use of long-acting beta-agonists (LABAs). There is evidence that beta2-agonists with higher intrinsic efficacy are more effective in relieving bronchoconstriction in the acute setting and that they could paradoxically cause patients to delay longer in seeking medical help.[30,31]

Reduced corticosteroid treatment

A slight but significant variation of the delay hypothesis suggests that patients who have separate beta2-agonists and corticosteroid inhalers may choose to take less corticosteroid because of better symptom control from the inhaled beta2-agonists, and it is reduced corticosteroid treatment that contributes to a rise in mortality. It is rather difficult to see how this hypothesis explains the epidemics of asthma deaths in the 1960s and 1970s relative to the 1920s and 1930s, given that corticosteroids were not used for the treatment of asthma in earlier decades. If this hypothesis was to explain increased mortality from more recent randomized controlled trial data, one would not expect to see an increase in mortality among those taking LABAs alone.[30,31]

Bronchodilators with ICS: A gold standard therapy

Epidemiological evidence has suggested a link between the use of beta2-agonists and increased asthma mortality. LABA monotherapy is not recommended in patients with asthma as it does not impact airway inflammation and is associated with an increased risk of morbidity and mortality. LABAs are only recommended when used in combination with ICS therapy. The combination of an LABA and an ICS is highly effective in reducing asthma symptoms and exacerbations, and is the preferred treatment option in adolescents or adults whose asthma is inadequately controlled on low-dose ICS therapy, or in children over 6 years old who are uncontrolled on moderate ICS doses. Although there is no apparent difference in efficacy between ICSs and LABAs given in the same or separate inhalers, combination ICS/LABA inhalers are preferred because they preclude the use of the LABA without an ICS, are more convenient, and may enhance patient adherence. Combination budesonide/formoterol has been approved for use as a single inhaler for both daily maintenance (controller) and reliever therapy in individuals 12 years old and older. It should only be used in patients whose asthma is not adequately controlled with low-dose ICS and who warrant treatment with combination therapy.[32,33] Consequently, in patients with a diagnosis or suspected diagnosis of asthma, measurement of FeNO can support the decision to start ICS but cannot be used to decide against treatment with ICS.[34,35]

Global Initiative for Asthma guidelines strong recommendations against use of bronchodilators or beta agonist without inhaled corticosteroids

Global Initiative for Asthma no longer recommends SABA-only treatment of asthma in adults or adolescents. Although inhaled SABAs are highly effective for the quick relief of asthma symptoms, patients whose asthma is treated with SABA alone (compared with ICS) are at

increased risk of asthma-related death and urgent asthma-related healthcare even if they have good symptom control. The risk of asthma exacerbations and mortality increases incrementally with higher SABA use, including in patients treated with SABA alone. One long-term study of regular SABA in patients with newly diagnosed asthma showed worse outcomes and lower lung function than in patients who were treated with daily low-dose ICS from the start. In adults, inhaled anticholinergic agents such as ipratropium are potential alternatives to SABA for routine relief of asthma symptoms; however, these agents have a slower onset of action than inhaled SABA. Oral SABA and theophylline have a higher risk of side effects and are not recommended. No long-term safety studies have been performed to assess the risk of severe exacerbations with these reliever medications in patients not also taking ICS. The use of long-acting muscarinic antagonists (LAMAs) in asthma without concomitant ICS is associated with an increased risk of severe exacerbations. The rapid-onset LABA, formoterol, is as effective as SABA as a reliever medication in adults and children, and reduces the risk of severe exacerbations by 15%–45% compared with as-needed SABA, but the use of regular or frequent LABA without ICS is strongly discouraged because of the risk of exacerbations.[36-40]

Underuse of rational inhalation therapy with inhaled corticosteroids in asthma in India

According to the 2019 Global Burden of Disease report, India contributes to an estimated 12.9% of global asthma cases (34.3 million) but a disproportionate 42.3% of all global asthma deaths.[5] In 2015, the Asthma Insights and Management survey highlighted the poor state of affairs regarding asthma management in India.[41] In one study, authors have documented that 43% of cases were difficult to accept COPD diagnosis, 91% of cases did not receive rational inhalation treatment, and 42% of cases were treated with oral medicines over rational inhalation treatment.[42] Most patients who get prescribed inhalers do not know how to use the device correctly, and among those who do, the majority do not use it correctly.[43]

Other treatment options available in asthma as "add on therapy"

Use of LAMAs in asthma

LAMAs such as tiotropium or glycopyrronium may be considered as add-on therapy if asthma is persistently uncontrolled despite medium- or high-dose ICS-LABA. Tiotropium reduces airflow obstruction by antagonizing muscarinic type-3 receptors on airway smooth muscles and submucosal glands, leading to bronchodilation and decreased mucus secretion. Adding LAMA to medium- or high-dose ICS-LABA modestly improved lung function but with no difference in symptoms. In some studies, adding LAMA to ICS-LABA modestly reduced exacerbations compared with some medium- or high-dose ICS-LABA comparators.[44-47] In a meta-analysis, there was a 17% reduction in the risk of severe exacerbations with the addition of LAMA to medium- or high-dose ICS-LABA.[48]

Add-on biologics

Omalizumab, a monoclonal antibody that binds with IgE, is indicated for moderate-to-severe persistent asthma in patients greater than or equal to 6 years old with a positive skin test or *in vitro* reactivity to a relevant perennial aeroallergen and symptoms that are inadequately controlled with ICSs. Omalizumab treatment of patients with poorly controlled severe asthma and total serum IgE levels of 30–700 IU/mL improved asthma control, reduced exacerbations, and reduced or did not increase the use of other medications.[49,50] Although omalizumab is indicated for use within this IgE-level range, there is some anecdotal evidence indicating that it can be successfully used outside of this range.[51,52] Strong evidence exists for the use of omalizumab in patients with Th2-high asthma phenotype. In post hoc analyses of pooled data from phase 3 trials, omalizumab reduced exacerbations in patients with high blood eosinophil counts (≥260 or ≥300 cells/μL) and high FeNO concentrations.[53]

Mepolizumab and reslizumab target IL-5, which promotes the recruitment of eosinophils from the bone marrow and their subsequent proliferation. Mepolizumab and reslizumab are indicated as add-on maintenance treatments for severe eosinophilic asthma in patients greater than or equal to 6 years old and adults greater than or equal to 18 years old, respectively.[54-56] Unlike mepolizumab, which is administered subcutaneously, reslizumab is only approved for intravenous administration. Both drugs are efficacious in eosinophilic asthma; however, the blood eosinophil count thresholds used in their respective pivotal trials were significantly different.

Benralizumab targets the IL-5 receptor α-subunit, thereby preventing the binding of IL-5 to its receptor, depleting eosinophils and basophils. It also enhances antibody-dependent, cell-mediated cytotoxicity as a consequence of its fucosylation. Benralizumab is indicated for the add-on maintenance treatment of patients with severe asthma greater than or equal to 12 years old and with an eosinophilic inflammatory phenotype. In phase 3 trials of benralizumab, efficacy was demonstrated in patients with baseline eosinophil counts greater than or equal to 300 cells/μL.[57,58]

Dupilumab inhibits the IL-4 and IL-13 pathways by binding to the IL-4 receptor α-subunit and prevents the downstream activation of effectors of these cytokines. Dupilumab is approved by the FDA as add-on maintenance treatment in patients greater than or equal to 6 years old with moderate-to-severe, eosinophilic asthma or with oral corticosteroid-dependent asthma, regardless of blood eosinophil count.[59] Dupilumab is, however, most efficacious in patients with blood eosinophil counts greater than or equal to 300 cells/μL, producing a 47.7% reduction in exacerbations and a 0.32 L increase in FEV1 in the pivotal clinical trial.[59]

Leukotriene-receptor antagonist

ICS agents have little effect on the formation or action of cysteinyl leukotrienes, inflammatory mediators in asthma. Leukotriene-receptor antagonists (LTRAs) have proved to be beneficial to double-blind, randomized, placebo-controlled trials.[60,61] Results of prior comparisons of LTRA and inhaled glucocorticoids, mostly double-blind, randomized, controlled trials, have been mixed, with some suggesting that LTRAs are less efficacious than inhaled glucocorticoids for patients with mild persistent asthma[62,63] and others reporting similar overall asthma control and proportions of patients meeting asthma-control criteria.[64,65] Results of randomized clinical trials indicate generally better improvements in lung function and symptoms and a reduction in the need for a short-acting bronchodilator with stepup therapy consisting of add-on LABA, as compared with add-on LTRA.[66,67] However, results of long-term trials (48 weeks) suggest that clinical outcomes such as exacerbations, hospitalizations, and rates of emergency treatment are similar to the two types of add-on therapy.[68]

Add-on azithromycin (three times a week)

Add-on azithromycin (three times a week) can be considered after specialist referral for adult patients with persistent symptomatic asthma despite high-dose ICS-LABA. Before considering add-on azithromycin, sputum should be checked for atypical mycobacteria, electrocardiogram should be checked for long corrected QT interval (and rechecked after a month on treatment), and the risk of increasing antimicrobial resistance should be considered.[69] Diarrhea is more common with azithromycin 500 mg three times a week.[70] Treatment for at least 6 months is suggested, as a clear benefit was not seen by 3 months in the clinical trials. The evidence for this recommendation includes a meta-analysis of two clinical trials in adults with persistent asthma symptoms that found reduced asthma exacerbations among those taking medium- or high-dose ICS-LABA who had either an eosinophilic or noneosinophilic profile and in those taking high-dose ICS-LABA.[70-72]

Theophylline in bronchial asthma

Theophylline (dimethylxanthine) has been used to treat airway diseases for more than 80 years. It was originally used as a bronchodilator, but the relatively high doses required are associated with frequent side effects, so its use declined as inhaled β2-agonists became more widely used. More recently, it has been shown to have anti-inflammatory effects in asthma and COPD at lower concentrations. The molecular mechanism of bronchodilatation is the inhibition of phosphodiesterase (PDE)3, but the anti-inflammatory effect may be due to the inhibition of PDE4 and histone deacetylase-2 activation, resulting in the switching off of activated inflammatory genes. Through this mechanism, theophylline also reverses corticosteroid resistance, and this may be of particular value in severe asthma and COPD, wherein histone deacetylase-2 activity is reduced. Theophylline is now usually used as an add-on therapy in patients with asthma not well controlled on ICSs with or without long-acting β2-agonists and in patients with COPD with severe disease not controlled by bronchodilator therapy. Side effects are related to plasma concentrations and include nausea, vomiting, and headaches due to PDE inhibition and at higher concentrations to cardiac arrhythmias and seizures due to adenosine A1-receptor antagonism. In the future, low-dose theophylline may be useful in reversing corticosteroid resistance in COPD and severe asthma.[73]

Add-on low-dose oral corticosteroids (≤7.5 mg/day, prednisone equivalent)

Add-on low-dose oral corticosteroids (≤7.5 mg/day, prednisone equivalent) may be considered for some adults with severe asthma, but they are often associated with substantial side effects. They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence to Step 5 treatment, and after exclusion of other contributory factors and other add-on treatments including biologics, where available and affordable. They should be assessed and monitored for risk of adrenal suppression and corticosteroid-induced osteoporosis.[74,75]

Bronchodilators without inhaled corticosteroids: More harm than benefit!

Smooth muscle cell proliferation hypothesis

Airway remodeling in asthma was first described in 1922 by Hubert and Koessler in cases of fatal asthma. Airway remodeling refers to the structural changes in the airways of asthmatic subjects not seen in healthy subjects. Structural changes include the loss of epithelial integrity, thickening of the basement membrane, subepithelial fibrosis, goblet cell and submucosal gland enlargement, increased smooth

muscle mass, decreased cartilage integrity, and increased airway vascularity.[75,76] Airway remodeling is clinically defined as persistent airflow obstruction despite aggressive anti-inflammatory therapies. ICSs form the basis of asthma therapy and are currently the most effective way to control airway inflammation. Proliferation and inflammatory mediators released in human lung fibroblasts can be reduced by the use of corticosteroids and by combining corticosteroids with beta-2 agonists.[77,78]

Sportsman's physiology hypothesis in asthma

Asthma airways behave similar to skeletal muscles in an athlete. In a similar way, in cases with Asthma, recurrent bronchoconstriction (contraction of smooth muscles) and bronchodilatation (relaxation of smooth muscles) will cause smooth muscle cell hyperplasia and later on hypertrophy. Smooth muscle cell pathology behaves exactly similar way to the skeletal muscles of athletes or sportsmen. Airway remodeling has a direct association with ongoing inflammation and a negative impact on asthma control. Only bronchodilators without ICS will result in symptomatic relief in asthma for a few days without impact on airway remodeling. As the duration of asthma illness increases, there will be more airway remodeling in the absence of ICS. It will cause more harm than benefit if no ICS is given, as it will cause smooth muscle endurance more aggressively by its pharmacological actions of bronchodilation in already-narrowed airways. These airway-related adverse events were more commonly documented with beta-agonists especially short-acting ones if timely ICS was not offered.

Recurrent exacerbator asthma phenotype and airway remodeling—probable link with bronchodilator use without ICS

"Exacerbation-prone phenotype" asthmatics are a cluster of patients who may suffer from more frequent and severe exacerbations than other asthmatics. Factors such as inadequate symptom control, improper adherence to medications, and incorrect use of inhalers are responsible for frequent asthma exacerbations. Improper adherence to medications leads to poor disease control, disease progression, emergency hospital visits, requirement for stronger medication, and increased healthcare costs.[79,80] Multiple studies and review articles posit airway remodeling as a principal cause of irreversible airway obstruction and the therapy-resistant component of airway hyperresponsiveness, noting the association of airway remodeling and rapid decline in lung function in individuals with severe asthma and modeling that predicts the effect of airway wall remodeling on airflow obstruction.[81-83]

Higher sputum eosinophil count (>25%) and sputum neutrophil count may be present in the "exacerbation-prone" patients because of the inability of the treatment to reduce inflammation in the airways.[84-86] Thus, only bronchodilators in the absence of ICSs will cause more harm than benefit. ICS has a key role in controlling eosinophilic inflammation and reducing exacerbations.

CONCLUSION

Bronchial asthma is an easily treatable and reversible airway disease with rational inhalation therapy with ICSs with bronchodilators. ICS is the gold standard therapy for asthma, which will change the natural course of illness by controlling inflammatory response and airway remodeling, which has a deleterious effect on the overall outcome. Only bronchodilators without ICS are causing more harm than any long-term benefit.

ICS with bronchodilators will change asthma outcomes and considered a "game changer," which will prevent exacerbations, cost of care due to it, emergency room visits, and ultimately mortality. Add-on therapies are available to control asthma, but these are costliest and less effective than most therapeutically effective and cost-effective ICS LABA combo.

Current recommendations as Maintenance and reliever therapy with ICS-formoterol are recommended treatment option in asthma due to its dual role as "rescue and reliever" in acute asthma exacerbations and ongoing chronic asthma care.

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Original Article

Comparative evaluation between collagen membrane (PerioCol®) and periosteum membrane in the treatment of gingival recession defects of maxillary anterior teeth: A clinical study

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Abstract

Background: The most common mucogingival defect is gingival recession (GR), which is characterized by apical displacement of the gingival margin from the cementoenamel junction and root exposure. Several techniques are available for treating GR and are collectively termed root coverage (RC) procedures. This study presents 3 months' results of a randomized clinical trial comparing RC in areas of isolated GR by coronally advanced flap (CAF) with periosteum membrane and PerioCol® membrane.

Materials and Methods: Twenty recession sites were selected for the study and further divided into two groups (Test group 1 [C AF + Periosteum membrane] and Test group 2 [CAF + Guided tissue regeneration membrane]) and completed the 3-month follow-up.

Result: Satisfactory result obtained after three months in both the cases but CAF+Periosteum showed better and fast healing.

Conclusion: Both treatment modalities showed a significant improvement in clinical parameters at 3 months postoperatively.

Keywords: PerioCol® membrane, periosteum membrane, recession coverage

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INTRODUCTION

Clinical dentistry deals with 50% esthetics and 50% focused on the treatment of pathological conditions of the tooth. The new generation has become more beauty conscious, so the demand of esthetic dentistry has increased. For a dentist, the esthetics of the oral cavity of the patient is the main factor to be concentrated on.

Periodontal disease is defined as a complex, multifactorial disease characterized by the loss of connective tissue attachment with destruction of periodontal tissues. Periodontal regeneration is a complex multifactorial process involving biologic events such as cell adhesion, migration, proliferation, and differentiation in an orchestrated sequence.[1]

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Gingival recession (GR) is a common manifestation in most populations. It is clinically manifested by an apical displacement of gingival tissue. It also leads to root surface exposure causing major functional and esthetic problems and has been related clinically to the higher incidence of attachment loss, hypersensitivity, and also root caries. It is a common occurrence and its prevalence increases with age.[2]

According to the American Academy of Periodontology's, position paper on mucogingival therapy, esthetic demands, reduction of root sensitivity, and management of root caries or cervical abrasions are the indications for root coverage (RC).[3] The ultimate goal of a RC procedure was to prevent, correct, or eliminate the recession defect with a good appearance related to the adjacent soft tissues and minimal probing depth (PD) following healing.[4]

Various surgical procedures are used in the treatment of recession defects.[5]

Pedicle soft tissue grafts

- Rotational flaps
- Laterally positioned flap
- Double papilla flap.

Advanced flaps

- Coronally positioned flap
- Semilunar flap.

Free soft tissue grafts

a. Nonsubmerged graft
   - One stage (free gingival graft)
   - Two stages (free gingival graft π coronally positioned flap).

b. Submerged grafts
   - Connective tissue graft + laterally positioned flap
   - Connective tissue graft + double papilla flap
   - Connective tissue graft + coronally positioned flap (subepithelial connective tissue graft)
   - Envelope techniques.

   - Root surface modification agents

- Enamel matrix proteins
- Guided tissue regeneration (GTR)
  i. Nonresorbable membrane barriers
  ii. Resorbable membrane barriers.

Coronally advanced flap (CAF) is a predictable mucogingival surgical procedure used to achieve RC in the treatment of Miller's Class I and Class II GRs. Best clinical outcomes in terms of RC are reported when the flap is passively adapted to the exposed root surface and the gingival margin is positioned at the cementoenamel junction (CEJ).[6]

The alveolar bone is covered by the periosteum and the endosteum. The adult human periosteum is highly vascular and is known to contain fibroblasts and their progenitor cells, osteoblast and their progenitor cells, and stem cells. The host periosteum can also be utilized as a barrier membrane with coronally repositioned flap. The use of autogenous periosteum has been widespread in the medical field and has shown promising results. It is a highly vascular connective tissue sheath containing numerous osteoblasts and osteoprogenitor cells, and the outer layer is composed of dense collagen fiber, fibroblasts, and their progenitor cells. It releases vascular endothelial growth factor which promotes revascularization during wound healing.[7]

GTR can be considered an effective and predictable surgical approach, which involves the placement of either resorbable or nonresorbable barrier to seclude a space around the diseased root surface and allow cells from periodontal ligament (PDL) and alveolar bone to repopulate the defect. GTR techniques utilize barrier membranes to facilitate the migration of bone cells and PDL cells to the defects by refraining soft tissue cells from penetrating it.[8]

This randomized control trial presents a comparison of CAF with the periosteum and GTR membrane for RC in maxillary anterior teeth with Class I and Class II recession defects.

MATERIALS AND METHODS

This clinical study is conducted to compare the RC in areas of isolated GR by CAF with periosteum membrane and PerioCol® membrane in the Department of Periodontology, Subharti Dental College and Hospital, Meerut, Uttar Pradesh. Clearance was obtained from the Ethical Committee of Swami Vivekanand Subharti University, Meerut, Uttar Pradesh. (Ethical approval no.–SDC/IEC/2020/669.[3]

Twenty recession sites were selected for the study and further divided into two groups (Test group 1 [CAF + Periosteum membrane] and Test group 2 [CAF + GTR membrane]). They were advised of the oral hygiene instructions. Informed written consent was taken from the selected individuals.

Criteria for selection

The following inclusion and exclusion criteria were used for the selection of patients.

Inclusion criteria

- Patients with age group between 20 and 60 years of either sex

- Patients who are free from systemic diseases
- Having good oral hygiene
- Having normal alignment of teeth in the arch
- Having at least Class I or Class II isolated GR in the maxillary anterior tooth region.

Exclusion criteria

- Class III or Class IV GR
- Patients with a history of allergic reactions
- The presence of severe cervical abrasion/root caries that would require restoration and the presence of abnormal frenal attachments
- Maxillary and mandibular molar teeth
- Pregnant and lactating patients
- Smokers.

Study design

Selected individuals were clinically examined for the type of GR present followed by the assessment of gingival biotype after administration of topical anesthetic agent. GR width and height were measured by surgical stent using UNC-15 probe and digital vernier caliper. The clinical parameters were assessed at different time intervals (at baseline, 1, and 3 months) in both groups. The following clinical parameters were recorded:

Plaque index

Based on criteria by Silness and Loe,[9] recordings were done at baseline, 1 month and 3 months.

Gingival index

Based on criteria by Loe and Silness,[10] it was evaluated at baseline, 1 and 3 months.

Gingival recession

The length and width of the recession were measured by means of a digital vernier caliper and the markings were rounded off to the first decimal place.

Width of keratinized gingiva

This was the distance from the gingival margin to mucogingival junction (MGJ) measured with the help of UNC-15 at baseline, 1 and 3 months.

Pocket probing depth

This was measured with Williams probe from the crest of gingival margin to the base of pocket at baseline, 1 and 3 months.

Clinical attachment level

This was measured by adding the pocket depth and distance from the gingival margin to the CEJ and was recorded at baseline, 1 and 3 months.

Root coverage percentage

The percentage of RC was calculated at baseline, 1 and 3 months. (Zucchelli and Sanctis).

$$\text{Root coverage \%} = \frac{\text{Preoperative VRD - Postoperative VRD} \times 100}{\text{Preoperative VRD (Vertical Recession Depth)}}$$

PRESURGICAL PROCEDURE

The compliance of each patient was sought. Scaling and root planing were carried out. Oral hygiene instructions were given mainly in terms of proper brushing technique. Three weeks following this initial therapy, the periodontal reevaluation was done for oral hygiene maintenance and to record gingival tissue response to the initial therapy. After reevaluation, preoperative parameters were recorded for each patient at baseline, and surgical procedure was carried out.

Preparation of the surgical site for both test groups

Adequate anesthesia with 2% lignocaine HCl containing 1:20,000 adrenaline was obtained at the surgical site. A CAF was designed using the following incisions: two obliques, divergent beveled incisions and intrasulcular, and crossed submarginal interproximal incisions.

In test group 1

After reflection of the mucoperiosteal flap an incision was made through the periosteum where the flap was still attached to bone, to create a partial thickness flap. The partial thickness flap was extended to expose a sufficient amount of the periosteum which was then separated from the underlying bone using a Glickman periosteal elevator.

The process of separating the periosteum was initiated at the apical extent of the periosteum, which was then lifted slowly in a coronal direction. The periosteum was not separated completely from the underlying bone, leaving it attached at its coronal most end. The periosteal pedicle graft (PPG) thus obtained was turned over the exposed root surface and sutured with a synthetic 5-0 bioabsorbable suture (polypropylene). After stabilizing, the periosteal graft, [Figure 1] flap was coronally positioned and sutured using a sling suture technique with a synthetic 5-0 bioabsorbable suture (polypropylene). The releasing incisions were closed with interrupted sutures.

In test group 2

A full-thickness trapezoidal flap was raised 3–4 mm apical to the osseous crest. A split-thickness flap was elevated to allow flap to move coronally without tension. Root surfaces

previously exposed at the oral cavity were thoroughly mechanically decontaminated using Gracey instruments. The PerioCol® GTR membrane was adapted and sutured around the recipient's teeth [Figure 2]. The membrane was trimmed to reach at least a level 2 mm apical bony margin. The CAF completely covered the membrane and fixed by sling sutures to accomplish a precise adaptation around teeth.

All the patients were prescribed with medications which included analgesic for 5 days twice daily (diclofenac potassium, paracetamol, and serratiopeptidase) and antibiotic for 5 days thrice daily (amoxicillin and potassium clavulanate) followed by probiotics for 5 days twice daily and antacid for 5 days once in the morning empty stomach.

Postoperative instructions

The following postoperative instructions were given to the patients:

1. Avoid taking hot foods and hard food for the first 24 h after surgery
2. Do not brush over the surgical area
3. On the day of surgery, apply ice intermittently on the face over the operated area
4. Rinse four to five times daily with povidone-iodine mouthwash for 1 week
5. If there is an unusual pain or bleeding from the operated site, come to the hospital immediately
6. Take the medication as prescribed.

Statistical analysis

All the values were expressed in the form of mean, standard deviation, and standard error of the mean. The parameters were compared between groups using Paired *t*-test for intragroup comparison and unpaired *t*-test for intergroup comparison at a similar time, i.e., baseline, 1 month and 3 months. The analysis was performed by the data analysis through IBM Statistical Package for the Social Sciences (SPSS) software.

RESULTS

During the course of the study, wound healing was uneventful. There were no postoperative complications or membrane perforation in any patients and none of the selected patients dropped out before the termination of the study.

Recession length and width were recorded postoperatively at the time interval of 1 month and 3 months for all patients using the UNC-15 probe and digital vernier caliper [Figures 3 and 4].

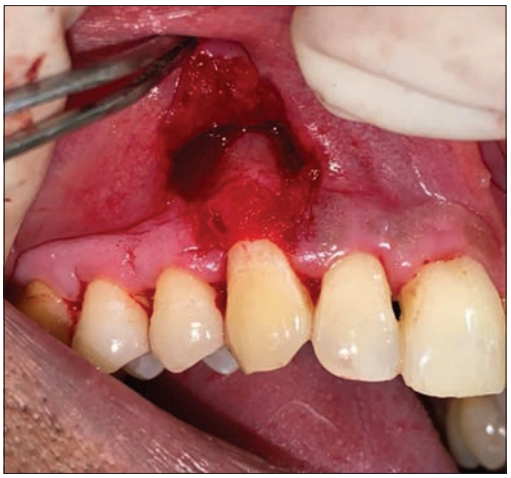

Figure 1: Periosteum membrane

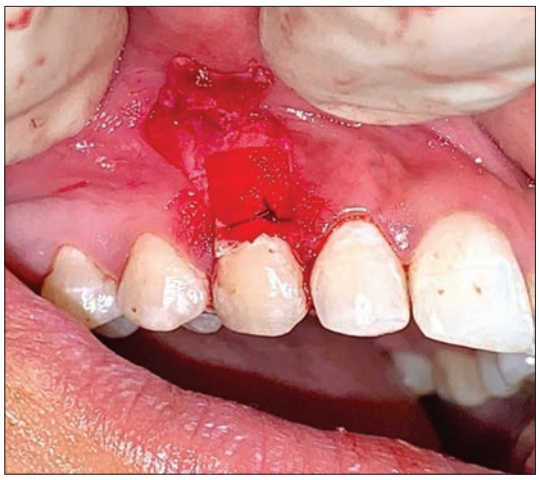

Figure 2: GTR membrane. GTR: Guided tissue regeneration

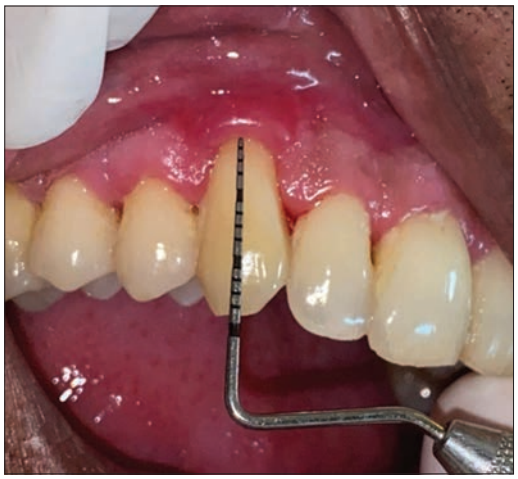

Figure 3: Three months postoperative CAF + Periosteum

Clinical parameters

A total of eight parameters were recorded, in which intragroup comparison was done using Paired *t*-test and intergroup comparison was done using unpaired *t*-test [Table 1].

The clinical attachment level, the width of keratinized gingiva (WKG), recession length, recession width, and RC percentage, in all these parameters significant differences ($P < 0.05$) were present between different time intervals (i.e., 0–1 month, 1–3 months, and 0–3 months) in both test groups, respectively. While when unpaired *t*-test was applied for the intergroup comparison between the two groups at baseline, 1 month and 3 months, the scores were found to be statistically nonsignificant ($P > 0.05$).

DISCUSSION

Mucogingival surgery is defined as "a periodontal surgical procedure to correct defects in the morphology, position, and/or the amount of gingiva."[11] The term has been changed since it was first introduced as surgery designed to correct problems such as pockets extending apical to the MGJ, malpositioned frenum, or inadequate width of attached gingiva. The term "periodontal plastic surgery," initially suggested by Miller in 1993, became accepted in modern periodontology to denote surgical procedures performed to prevent or correct anatomic, developmental, traumatic, or disease-induced defects of the gingiva, alveolar mucosa, or bone.[12]

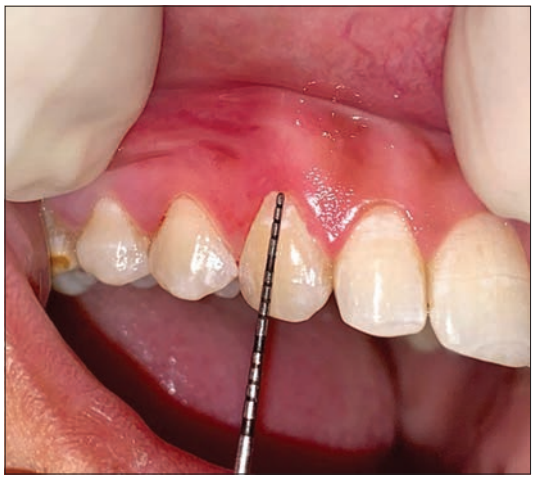

Figure 4: Three months postoperative GTR

The therapeutic goal in most cases of denuded roots is to restore the gingival unit at or near the CEJ.[13] The majority of these procedures consist of periodontal plastic surgical graft (mucogingival) techniques, either alone or in combination with guided tissue regenerative procedures.

PPG for the treatment of GR defect was used by Mahajan.[14] At the end of 1 year, the recession defect was completely covered because the rich vascularity of the periosteum prevents its necrosis and makes it a suitable graft over the avascular root surface. Buccal grade II furcation defect in the lower molar was treated with the periosteal membrane, as a barrier membrane by Verma *et al*.[15] After 6 months, the mean gain of vertical and horizontal bone levels was 1.67 mm and 1.50 mm, respectively. The vascularized periosteum membrane can be used for recession coverage in a similar way as to a connective tissue graft and can be epithelialized by the neighboring mucosa as a vital and well-vascularized tissue.

Table 1: The probable values of paired *t*-test between successive time intervals in the control group and test group for all parameters (intragroup/within group comparison)

Parameters	Test Group-1				Test Group-2			
	0–1	1–3	0–3	Percentage improvement (0–3)	0–1	1–3	0–3	Percentage improvement (0–3)
GI	0.5241** *P*>0.05 (NS)	0.3214** *P*>0.05 (NS)	0.4185** *P*>0.05 (NS)	51.505	0.2485** *P*>0.05 (NS)	0.1554** *P*>0.05 (NS)	0.0998** *P*>0.05 (NS)	49.957
PI	0.7112** *P*>0.05 (NS)	0.2189** *P*>0.05 (NS)	0.2332** *P*>0.05 (NS)	23.36	0.1885** *P*>0.05 (NS)	0.3210** *P*>0.05 (NS)	0.4128** *P*>0.05 (NS)	18.592
Probing pocket depth	0.2414** *P*>0.05 (NS)	0.1998** *P*>0.05 (NS)	0.0058* *P*<0.05 (significant)	65.00	0.2147** *P*>0.05 (NS)	0.1663** *P*>0.05 (NS)	0.0365* *P*<0.05 (significant)	88.89
CAL	0.3221** *P*>0.05 (NS)	0.0000* *P*<0.05 (significant)	0.0058* *P*<0.05 (significant)	38.83	0.0047* *P*<0.05 (significant)	0.0022* *P*<0.05 (significant)	0.0039* *P*<0.05 (significant)	46.52
Depth of keratinized gingiva	0.0003* *P*<0.05 (significant)	0.0190* *P*<0.05 (significant)	0.0000* *P*<0.05 (significant)	88.43	0.0000* *P*<0.05 (significant)	0.0273** *P*<0.05 (significant)	0.2847* *P*<0.05 (significant)	62.80
Recession length	0.0000* *P*<0.05 (significant)	0.0015* *P*<0.05 (significant)	0.0052* *P*<0.05 (significant)	88	0.0000* *P*<0.05 (significant)	0.0013* *P*<0.05 (significant)	0.0000* *P*<0.05 (significant)	77.6
Recession width	0.0000* *P*>0.05 (significant)	0.0046* *P*<0.05 (significant)	0.0084* *P*<0.05 (significant)	70.19	0.0031* *P*<0.05 (significant)	0.0135* *P*>0.05 (significant)	0.0000* *P*<0.05 (significant)	68.63
RC (%)	0.0000* *P*<0.05 (significant)	0.0000* *P*<0.05 (significant)	0.0000* *P*<0.05 (significant)	92.53	0.0000* *P*<0.05 (significant)	0.0000* *P*<0.05 (significant)	0.0000* *P*<0.05 (significant)	88.77

*Shows a significant difference between different time intervals at 0.05 level of significance $P<0.05$, **Shows no significant difference between different time intervals at 0.05 level of significance $P>0.05$. NS: Nonsignificant, GI: Gingival index, PI: Plaque index, RC: Root coverage, CAL: Clinical attachment level

The advantages of the periosteum eversion technique in comparison to all other techniques using the free soft tissue graft are no donor site morbidity, periosteum harvested as much as required because periosteum exits in every location of alveolar bone and lowest risk of infection, necrosis, and graft removal because well-vascularized periosteum has the least possibility to react to bacterial contamination like any other vital tissue.

Singh and Kiran[16] presented a case report on the periosteum eversion technique for coverage of the denuded root surface. It concluded that the periosteum eversion technique is the predictable technique for the treatment of GR. At the end of 6 months, 100% root surface was covered successfully with 5.0 mm of gingival height and 1.0 mm of PD which is similar to our study. On the other hand Jain *et al*.[17] presented a comparative study on the periosteum eversion technique with GTR membrane as a graft with CAF in the treatment of GR defects. The end point of their study reported that periosteum techniques achieve better esthetics and RC when compared to the coronally positioned flap with GTR technique. Whereas covering the teeth with receded gingiva, both techniques are considered appropriate, as has also been noted in the present study.

PerioCol® is a sterile type 1 collagen membrane of fish origin. It is derived from specially controlled and certified animals and is highly purified to avoid any antigenicity. Collagen is a major constituent of the natural extracellular matrix (ECM). It has many biological activities such as hemostatic ability, attraction and activation of PDL and gingival fibroblast cells, and augmentation of tissue thickness, biocompatibility, biodegradability, and cell affinity. These properties render it advantageous for extensive application and as an ideal choice for a bioresorbable GTR or GBR barrier membrane. Most of the commercially available collagen membranes are developed from type I collagen or a combination of type I and type II.[18]

In a study, eight nonsmoking healthy controls with Miller's Class I and II recession defects in the maxillary anterior region were selected. The patients were treated with coronally repositioned flap along with PerioCol® membrane. Three-month postoperative measurements demonstrated significant RC and a reduction in the recession depth and width. In addition, there was a significant increase in the WKG and the attached gingiva.[19] The findings of this study correlate with the results of the present study.

Many authors have treated Miller classes I or II GR with GTR membrane It was noted that there was a significant difference ($P < 0.05$) was present between different times, respectively. While when unpaired *t*-test was applied the scores were found to be statistically nonsignificant ($P > 0.05$) which correlates with the results of the present study.[20]

As like in any study, this clinical study of the periosteum eversion technique and GTR membrane has certain limitations. The technique, although simple, needs surgical dexterity for the operator, especially during the reflection of the periosteum, which is firmly attached to the underlying bone and during the separation of periosteum from submucous connective tissue as there may be chances of tear or perforation of flap and managing the stabilization of PerioCol® membrane with suture as chances of tear of the membrane. There are less evidence-based studies present where the comparison of both membranes is done together.

CONCLUSION

It can be concluded that a periosteal membrane and GTR membrane both offer a successful and viable alternative for the coverage of GR defect as both techniques are considered appropriate for coverage of exposed root.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Effectiveness of BCG in recurrent non-muscle invasive bladder tumor: A 10 year retrospective study from a tertiary care centre

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Abstract

Introduction: Cancer-a term a word used to be so rare five decades back that people didn't even know about this but now it has become so common and rampant and interestingly can be compared to a devil whose size seems to be increasing progressively. Even after so much advancement in medical science we have not been able to catch its tail. Urinary Bladder one of the very common cancer in our urological domain with its subtype non-muscle invasive bladder cancer (NMIBC) having high recurrence and progression rates has become very interesting subject for research.

Such features led investigators to study the use of drugs to prevent this, out of which Bacillus Calmette–Guerin (BCG) has been successfully used as an intra vesical therapy to prevent recurrence and progression in NMIBC for more than four decades.

Materials and Methods: In our study we have analyzed 111 patients retrospectively with only recurrent urinary bladder tumor irrespective of treatment received in the past. After completion Trans Urethral resection of bladder tumor (TURBT) and re-staging TURBT to substantiate the stage, induction and maintenance course of intravesical BCG was given according to Lamm protocol & the impact of this therapy was studied in regards to recurrence free, progression free, cystectomy free & overall survival rates.

Result: Out of 111 patients, sixty percent of patient remained disease free, 19 patients had stage progression, nine patients underwent radical cystectomy and there was three cancer specific death.

Conclusion: Despite BCG being the gold standard treatment for NMIBC, still intense research is required as there is a wide dark area of BCG failure.

Keywords: Non muscle invasive bladder cancer, Trans urethral resection of bladder tumor, intra vesical BCG, immunotherapy, recurrence

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INTRODUCTION

Bladder cancer is said to be the seventh most commonly diagnosed cancer in the male population worldwide while it is tenth when both the genders are considered.[1] The worldwide age-standardized incidence rate and mortality rates for both genders vary across countries

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due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are however partly caused by different methodologies used and quality of data collection.[2]

At diagnosis, detrusor muscle is not involved in 70%–85% of bladder cancers. This noninvolvement of detrusor muscle gives way for bladder sparing therapies since this is considered as the most crucial point in the treatment of non muscle invasive bladder cancer (NMIBC). The high incidence of recurrence (50%-80%) of this diseases and further progression to muscle invasion (up to 30%) mandates close patient follow up and even aggressive treatment in some conditions.[3]

Till date Bacillus Calmette-Guerin as an immunotherapy has been most successful in the treatment of urothelial carcinoma representing gold standard care.[4]

So far studies have been reported where all the cases of primary or recurrent bladder tumor patients are included to study the impact of intravesical BCG administration and their average recurrence-free survival, progression-free survival, and diseases-free survival rate.

In our research we have included the patients only with NMIBC recurrent bladder tumor irrespective of the treatment they have received for the primary tumor except early partial / radical cystectomy so to study the tolerability and effectiveness of BCG in preventing recurrence, further progression and also to determine cancer specific death, cystectomy-free survival and over-all survival.

MATERIALS AND METHODS

From 2007 to 2017 data of all patients with their demographic profile, previous medical and surgical history, and smoking habits were tabulated in an MS-Excel sheet and were thoroughly examined. These patients were offered intravesical BCG therapy at our institution and were reviewed.

Our inclusion criterion included all those patients who had histo-pathologically proven transitional cell carcinoma of the urinary bladder pTa/pT1 with or without coexisting carcinoma *in situ* (CIS) with previous history of trans urethral resection of bladder tumor (TURBT) irrespective of treatment received post previous TURBT. Our exclusion criterion included all those patients whose age was more than 85 years, immunocompromised, incontinent bladder, or had a h/o BCG sepsis or having muscle invasive bladder cancer.

According to our institutional protocol, intravesical BCG therapy was given to all patients. Complete TURBT and restaging TURBT were done to remove any residual tumor and to substantiate the stages of disease within 6 weeks before initiating intravesical BCG to all patients even including pT1 and pTa. Once the restaging is done intravesical BCG therapy was initiated after 2–3 weeks. The BCG strain used was Moscow strain. Depending on the availability of strains at our institute, and in order to keep ensuring a steady supply, the choice of strain was made.

10 French infant feeding tube was placed per urethral and re-suspended BCG powder with 50 mL of 0.9% normal saline introduced via it in the bladder. Patients were asked to hold on the urine for 2 h before emptying the bladder. Patients were also advised not to take oral fluid 4 h before and 2 h after each therapy session.

Induction course comprised having one instillation every week for 6 subsequent weeks whereas the maintenance course comprised weekly dose for 3 weeks given at 3, 6, 12, 18, 24, 30, and 36 months from starting of induction therapy according to Lamm *et al*.[5] protocol which was followed in our institute with no evidence of disease after the re-staging TURBT. Intravesical BCG of 80 mg was given for both induction and maintenance therapy.

Cystoscopy was performed at every 3 months for the initial 2 years, and then at every half yearly for the subsequent 2 years, followed by annually thereafter. If recurrence occurs at any time then cystoscopy is rescheduled at every 3 months after RE-TURBT.

RESULTS

It is a retrospective analysis of 111 patients with recurrent bladder tumor and the impact of intra-vesical BCG was studied after the exclusion of those who did not meet the criterion.

111 patients with median age of 56 years with range of 35–82 year with mean 57.49 year were evaluated [Table 1]. Our study had 12 (10.81%) female patients and 99 (89.18%) male patients. Smoking habits of the patients were also taken into consideration and it was found that 43 (38.73%) were ex-smokers, 16 (14.41%) were non-smokers, and 52 (46.84%) were smokers. Forty-five (40.54%) patients were of high grade on histology and remaining 66 (59.45%) were consisted low grade. This study included 98 (88.28%) patients with stage T1 and 13 (11.71%) patients with stage pTa with or without CIS. Median follow-up was 3.87 year

(range 7 months–9 years, mean 4.2 year). According to the protocol followed by our institution, 71 (63.96%) patients had completed the BCG protocol and 40 (36.03%) patients required termination due to various reasons described. Twenty-two (55.0%) patients had BCG intolerance, seven (17.50%) patients had BCG resistance, nine (22.50%) patients had BCG refractory and two (5.0%) patients developed BCG sepsis in the form of systemic infection with persistent high-grade fever and positive culture for BCG. These patients required antitubercular therapy and BCG therapy was discontinued.

Table 1: Demographic data

Gender	Female		12	10.81%
	Male		99	89.18%
Smoking	Ex-smoker		43	38.73%
	Non smoker		16	14.41%
	Smoker		52	46.84%
Stage	T1		98	88.28%
	Ta		13	11.71%
Grade	High grade		45	40.54%
	Low grade		66	59.45%
BCG	BCG complete		71	63.96%
	BCG termination		40	36.03%
	Reasons for BCG termination	BCG refractory	09	22.50%
		BCG intolerance	22	55.00%
		BCG resistance	07	17.50%
		BCG sepsis	02	05.00%

Table 2: Disease outcome

Diseases recurrence	No		66 (59.45%)
	Yes		45 (40.54%)
	Histology of recurrence	T a low grade	9 (20.00%)
		T a High Grade	16 (35.55%)
		T 1 High grade	20 (44.44%)
Diseases progression	No		92(82.88%)
	Yes		19(17.11%)
	Histology	T1 high grade	12(63.15%)
		T2	7 (36.84%)
	Salvage therapy	Radical cystectomy	9 (8.10%)
Outcome	Alive		108 (97.29%)
	Death		3 (2.70%)

Sixty-six (59.45%) out of 111 patients remained free of recurrence during entire follow-up period, whereas the remaining 45 (40.54%) patients had recurrence at different time with median of 9 months and range 3–72 months, out of these 45 patients, 36 (80.00%) developed recurrence within first year, eight patients (17.77%) developed between 2 and 4 years and rest one (2.22%) patient developed recurrence after 4 years of follow-up [Table 2]. Kaplan–Meier curve [Table 3] for the recurrence-free survival showed that maximum recurrence occurred within first year and most of the remaining had within next three years with last one in sixth year.

Nineteen (42.22%) patients out of these 45 patients had stage progression during follow-up with median of 6 months and range 3–21 months. Sixteen (84.21%) patients had stage progression within first year of follow-up and rest three (15.79%) developed after 1 year of follow-up.

Analysis of Kaplan–Meier curves for progression-free survival demonstrated that all progression occurred within first 2 years [Table 4].

During the period of follow-up patients who developed progression or have had any reasons for BCG termination (resistance/refractory/relapse) were counselled and offered treatment options such as radical cystectomy. Since our study is a retrospective one, it was seen that radical

Table 3: Kaplan–Meier survival analysis curve of disease-free survival

Total *N*			111
No of events			45
Censored	*N*		66
	Percent		59.46%
DFS at the end of 3 years			59.82%
DFS at the end of 5 years			59.82%
DFS at the end of the study			58.20%
Mean	Estimate		67.9324
	Standard error		4.63365
	95% confidence interval	Lower bound	58.8504
		Upper bound	77.0143

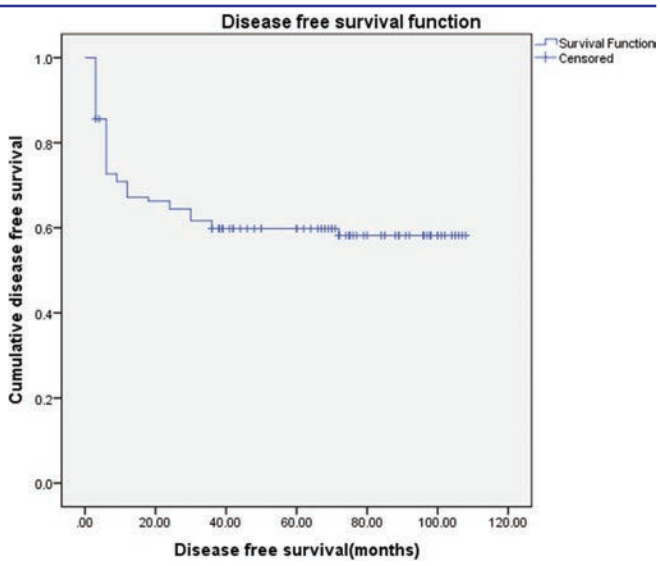


Table 4: Kaplan–Meier survival analysis curve of progression-free survival

Total *N*			111
No of events			19
Censored	*N*		92
	Percent		82.88%
PFS at the end of 3 years			82.27%
PFS at the end of 5 years			82.27%
PFS at the end of the study			82.27%
Mean	Estimate		90.5302
	Standard error		3.64264
	95% confidence interval	Lower bound	83.3906
		Upper bound	97.6697

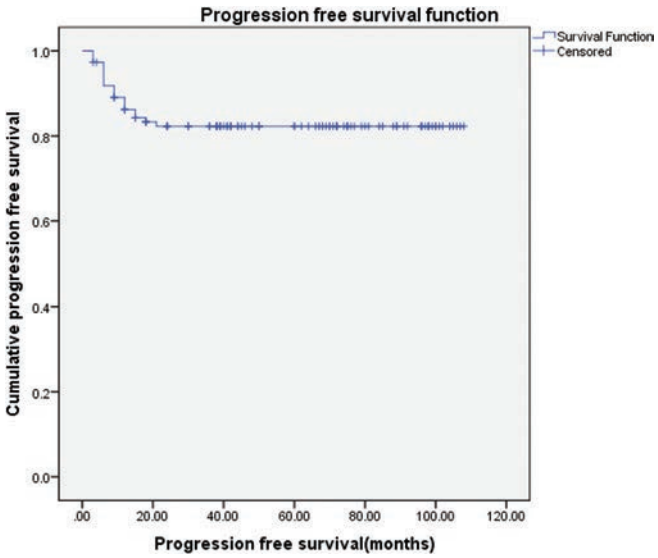
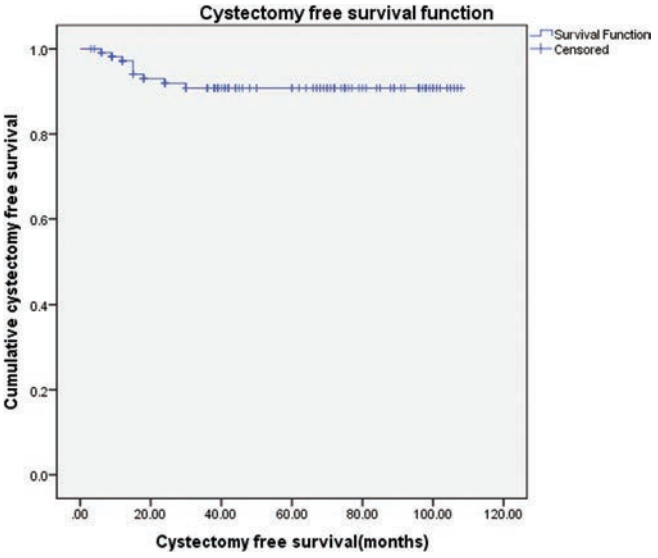


Table 5: Kaplan–Meier survival analysis curve of cystectomy-free survival

Total *N*			111
No of events			9
Censored	*N*		102
	Percent		91.89%
CFS at the end of 3 years			90.78%
CFS at the end of 5 years			90.78%
CFS at the end of the study			90.78%
Mean	Estimate		99.5572
	Standard error		2.68705
	95% confidence interval	Lower bound	94.2905
		Upper bound	104.824



cystectomy was done on nine (8.10%) patients all within 30 months of commencement of treatment [Table 5].

There were three cancer specific death at a mean follow-up of 4.2 years and overall survival was 96.75% [Table 6]

DISCUSSION

For NMIBC, standard treatment of choice is TURBT and cystoscopic follow-up. After the same, without further intervention the most significant problem encountered with NMIBC is recurrence and progression requiring the need for adjuvant treatment.

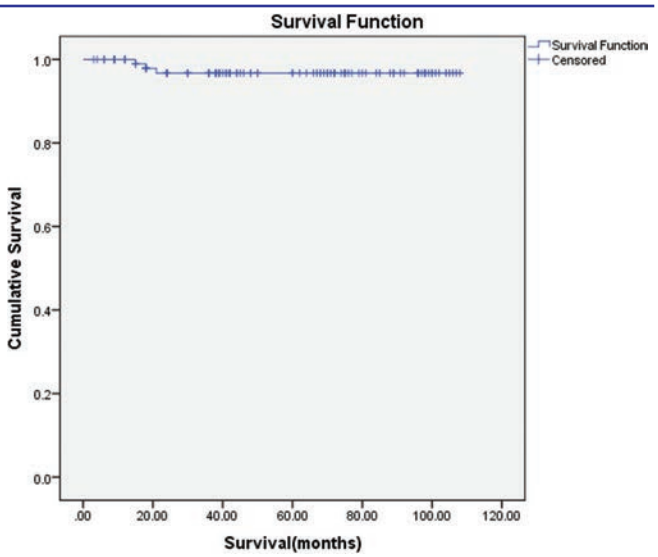
The unavoidable high recurrence and progression rates of NMIBC have led the researchers to study the use of different modalities so as to prevent or slow down the recurrence of NMIBC.

Disease progression was explained in our study as any deterioration of disease parameters including step up of pTa low grade to high grade or to pT1 or detection of pT2 stage during follow-up.

Cystectomy being suggested to all patients who either progressed or developed deteriorating disease parameters or BCG resistant or BCG refractory.

Table 6: Kaplan–Meier survival analysis curve of overall survival

Total *N*			111
No of events			3
Censored	*N*		108
	Percent		97.30%
OS at the end of 3 years			96.75%
OS at the end of 5 years			96.75%
Mean	Estimate		105.074
	Standard error		1.66184
	95% confidence interval	Lower bound	101.817
		Upper bound	108.332



The mechanism of action of BCG is not easy to understand. In brief, it is likely that BCG antitumor immunotherapy may be the consequence of the immune response which was initially aimed at the clearing the foreign pathogen present in the bladder. The end result, therefore, is an activated immune response required to combat the weakened mycobacteria, which is necessary to target tumor cells.[6-9]

This explanation is summarized by and is being explained in different steps by Redelman-Sidi *et al.*[10] the first step is the control against mycobacteria followed by second step that is control against tumor cells. BCG first needs to attach to the urothelium via fibronectin and integrins. The antigen 85 complex of mycobacteria including BCG plays a pivotal role in synthesizing major components of the both leaflets that is inner and outlet leaflets of mycobacterial outer membrane and binds to fibronectin. BCG after attachment with urothelium via fibronectin[11,12] internalized and further captured by innate response cells. Antigen presentation and cytokine release lead to major histocompatibility complex II upregulation and of IL-6, IL-8, and granulocyte-macrophage colony stimulating factor (GM-CSF). Immune cells are then engaged to the war zone including granulocytes, CD4 and CD8T cells, natural killer cells, and macrophages. A series of cells mainly TH-1 cytokines including Interferon gamma, IL-1, IL-12, IL-18, IL-23, and tumor necrosis factor-alpha are produced by these immune cells. This response is although nonspecific.

BCG culture filtrate and whole BCG can be found in the peripheral blood of patients with NMIBC treated with BCG indicating some specific immune response against various BCG subfractions.[11] Local immune responses are manifested as granulomas, which can be seen in the bladder wall of these patients treated with BCG.

As superfluity is a keyword in biology, it looks as if the immunological complexity of live attenuated mycobacteria is required to trigger the avalanche of immune responses needed to clear and control tumor cells locally in the bladder. Response to BCG therapy, either positive or negative is driven by a combination of many parameters such as the activation of innate immune pathways.

The well-known gene encoding natural resistance-associated protein 1 (NRAMP 1) exists in two allelic forms, which differ from each other by a point mutation. Polymorphism in NRAMP 1 and hGPX1 gene to BCG has led to reduce cancer-specific survival for the NRAMP1 D543N G:G genotype, as well as decreased recurrence-free survival attenuated risk of recurrence post-BCG.[13]

Sylvester *et al.*[14] did a meta-analysis of seven RCTs which showed that 36.7% patients who received a single postoperative instillation of epirubicin, mitomycin C (MMC), thiotepa, or pirarubicin had recurrence as compared to 48.4% who had not received any adjuvant treatment, there was a decrease of 39% in the odds of recurrence (OR 0.61, $P < 0.0001$). It was also seen that for the patients with multiple tumors, a single instillation is not enough. Thus, a need for prolonged adjuvant treatment emerged.

Among the various drugs considered for adjuvant treatment for slowing down recurrence in NMIBC, BCG was one alternative as it showed antitumor activities in several

different cancers including urothelial cancer. The initial regimen, which was studied, included percutaneous dosing which later modified to intravesical dosing.[15]

Duchek *et al.*[16] also stated in his study, the superiority of intravesical BCG to combination of epirubicin and interferon-alpha 2b in preventing recurrence in a randomized multi centric trial wherein patients were given an induction course followed by two years maintenance course.

A meta-analysis by Malmström *et al.*[17] and colleagues that intravesical BCG with maintenance course when given to 2820 patients for nine trials and comparing the same with intravesical MMC has recurrence risk reduction for around 32% which is significant and hence it was concluded in the study that for prophylaxis of recurrence, maintenance BCG was needed to be more effective than MMC.

Since then, BCG became the most important part of this treatment protocol and is being used successfully for this indication to treat NMIBC, and it has been now more than four decades till today.

Han *et al.*[18] performed a meta-analysis which stated that there is statistically significant difference in the odds ratio (OR 0.61, $P < 0.0001$) for tumor recurrence between the BCG and nonBCG treated groups. Shelley *et al.*[19] concluded in a meta-analysis showed that BCG therapy was superior to resection alone for the prevention of NMIBC recurrences. Sylvester *et al.*[20] demonstrated in a meta-analysis that intravesical BCG was not only effective in reducing recurrence but significantly reduces the risk of progression also in NMIBC patients receiving BCG maintenance. The European 0rganisation for research and treatment meta-analysis suggested that there are no large differences in efficacy between various BCG strains.

The accentuation on the usage of BCG in combination with maintenance in NMIBC treatment was further described by Lamm *et al.*[5] in their study where recurrence occurred in 40% and progression of disease occurred in 24% with a median follow-up of 98 months in a study of 192 patients.

Till date there have been numerous studies explaining the use of BCG in all cases including primary or recurrent NMIBC. Our study is exclusively based on recurrent NMIBC and the role of intravesical BCG in the same.

In our study, recurrence occurred in 45 (40.5%) with median time of 9 months and range 3–72 months and stage progression occurred in 19 (17.11%) with median time of progression is 6 months and range 3–21 months.

CONCLUSION

In patients having intermediate and high-risk NMIBC, BCG has been the gold standard option for treatment. Even after four decades of use, the exact pharmacodynamics of BCG remains unclear, in spite of all these, the future of BCG looks promising when it comes to preventing recurrence and progression as still no alternative therapy has been found as effective.

The area of BCG failure has been the concern of intense research activity as at present there is no better option for intravesical treatment. Hopefully further research for new intravesical therapies or introduction of immune checkpoint blockade agents might fulfil this unmet need.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Role of interleukin-6 in COVID-19 pneumonia as marker of cytokine storm and predictor of course during hospitalization: Prospective, observational study in tertiary care setting in India

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Abstract

Background: Robust data on interleukin-6 (IL-6) are available in bacterial infection as marker of inflammation, and now it can be utilized in currently ongoing coronavirus disease-19 (COVID-19) pneumonia pandemic to guide treatment strategy as marker of inflammation.

Methods: Prospective, observational, and 12 weeks' follow-up study, included 2000 COVID-19 cases confirmed with reverse transcription–polymerase chain reaction. All cases were assessed with lung involvement documented and categorized on high-resolution computed tomography (HRCT) thorax, oxygen saturation (SpO2), IL-6 at the entry point, and follow-up. Age, gender, comorbidity, and bilevel positive airway pressure/noninvasive ventilation (BIPAP/NIV) use and outcome as with or without lung fibrosis as per CT severity. Statistical analysis is done by the Chi-square test.

Results: In a study of 2000 COVID-19 pneumonia cases, age (<50 and >50 years) and gender have a significant association with IL-6. HRCT severity score at entry point has a significant correlation with IL-6 level ($P < 0.00001$) IL-6 level has a significant association with duration of illness ($P < 0.00001$). Comorbidities have a significant association with IL-6 level ($P < 0.00001$). IL-6 level has a significant association with SpO2 ($P < 0.00001$). BIPAP/NIV requirement has significant association with IL-6 level ($P < 0.00001$). Timing of BIPAP/NIV requirement during the course of hospitalization has significant association with IL-6 level ($P < 0.00001$). Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in post-COVID lung fibrosis ($P < 0.00001$). Follow-up IL-6 titer during hospitalization as compared to entry point normal IL-6 has significant association in post-COVID lung fibrosis ($P < 0.00001$). Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in predicting cytokine storm irrespective normal or abnormal of IL-6 at the entry point ($P < 0.0001$).

Conclusions: IL-6 is sensitive and reliable marker of inflammation helped in predicting cytokine storm COVID-19 pneumonia by analyzing sequential titers. Il-6 has very important role in predicting severity of illness, progression of illness, and need for ventilatory support. Sequential IL-6 titers predicted course during hospitalization and final radiological outcome as post-COVID ling fibrosis or post-COVID sequelae.

Keywords: Coronavirus disease-19 pneumonia, inflammatory marker, interleukin-6, oxygen saturation

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INTRODUCTION

Coronavirus disease-19 (COVID-19) is first coronavirus-related global pandemic caused by novel severe acute respiratory syndrome coronavirus-2, and rapid evolution of pandemic has resulted in fast-track developments in antivirals, medical management, and vaccination for use to prevent morbidity and mortality. Although Lung is the primary target organ involvement in COVID-19, many patients were having pulmonary and extrapulmonary manifestations of diseases variably as a resultant pathophysiological effects of the immune activation pathway and direct virus-induced lung damage. In COVID-19 pneumonia, pathophysiology constitutes different pathways such as immune activation, inflammatory, thrombogenic, and direct viral affection to lungs and extrapulmonary tissues.[1]

The International Federation of Clinical Chemistry and Laboratory Medicine Task Force on COVID-19 has been established to synthesize up-to-date information on the epidemiology, pathogenesis, and laboratory diagnosis and monitoring of COVID-19, as well as to develop practical recommendations on the use of molecular, serological, and biochemical tests in disease diagnosis and management.[2,3]

Interleukin-6 (IL-6) was found in 1973 as a soluble factor that is secreted by T cells and is important for antibody production by B cells.[4] Since its discovery, the role of IL-6 in immune regulation and dysregulation in many diseases has been studied in the past 50 years. Before COVID-19, this molecule has been studied in rheumatoid arthritis, Crohn's disease, ulcerative colitis, multiple myeloma, systemic juvenile idiopathic arthritis, Castleman's disease, ankylosing spondylitis, psoriatic arthritis, and other immune dysregulated diseases. Robust data are available regarding its abnormally elevated levels of IL-6 in local tissue and serum of these cases due to dysregulated immune function and targeted therapy against this novel molecule is now considered as a best disease-modifying approach rather than conventional steroids in these cases.[5-7]

The role of IL-6 as marker of the dysregulated immune system is the earliest reports from China in the initial period of the COVID-19 pandemic by Huang *et al*.[8] they also mentioned that IL-6 is can be used with other inflammatory markers such as C-reactive protein (CRP) and Ferritin. Leisman *et al*.[9] documented that IL-6 is raised in COVID-19, but its level is not as high as documented in sepsis. Chen *et al*.[10] documented that, 2000-fold increase in IL-6 level in COVID-19 pneumonia cases requiring intensive care unit hospitalization. The U.S. FDA[11] had approved IL-6 analysis during workup of COVID-19 pneumonia in June 2020, since then many laboratory companies came up with their methodology of IL-6 assay during the COVID-19 pandemic. Hypercytokinemic immune dysregulation in COVID-19 is known as cytokine storm syndrome. IL-6 levels ≥80 pg/mL predict an increased risk of respiratory failure and death, and immunomodulatory therapy is an area of urgent investigation.[11]

In the present study, we have utilized IL-6 as a basic inflammatory marker in laboratory panel workup in all COVID patients and analyzed it as "core marker" during follow-up in all admitted patients to assess the progression of illness and its role in assessing the final outcome.

METHODS

Data source

This study was approved by the Institutional Review Board/Ethics Committee at Venkatesh Hospital and Critical Care Center Latur India and MIMSR Medical college Latur India, (Approval # VCC/81-2020-2021; Approval date July 29, 2020).

Methodology

Prospective, observational study conducted from July 2020 to May 2021 in MIMSR Medical College and Venkatesh Hospital Latur India, included 2000 COVID-19 cases admitted to indoor unit confirmed with reverse transcription–polymerase chain reaction (RT-PCR) to find out the role of IL-6 in predicting the severity of illness, assessing response to therapy and outcome as post-COVID fibrosis [Figure 1].

Inclusion criteria

COVID-19 patients confirmed with RT-PCR, above the age of 18 years, hospitalized in the study centers, including those with comorbidities and irrespective of severity and oxygen saturation (SpO2) were included in the study.

Exclusion criteria

Those not willing to give consent, not able to perform CRP, and not willing to remain in follow-up, and cases who died during hospitalization or before 12 weeks of discharge from hospital were excluded.

Study design

Prospective, observational, 12 weeks follow-up study.

All study cases were undergone the following assessment before enrolling in study

COVID-19 RT-PCR test was performed on nasopharyngeal samples collected with all standard institutional infection

control policies. If the first test results were negative and radiological features clearly documenting pneumonia then we have repeated RT-PCR test and finally, we enrolled all cases with positive COVID-19 RT-PCR test result. High-resolution computed tomography (HRCT) Thorax to assess the severity of lung involvement as per COVID-19 Reporting and Data System,[12] and categorized as mild if score <7, moderated if score 8–15 and severe if score >15 or 15–25. Clinical assessment, routine laboratory biochemistry, and hematological workup with viral inflammatory markers such as CRP, Ferritin, lactate dehydrogenase (LDH), IL-6 titers were done in all cases. Entry point IL-6 titer was utilized as assessment tool of the severity of illness with clinical parameters. If IL-6 analysis was normal at entry point, then IL-6 titer was repeated on the day of discharge from the hospital or done during hospitalization if clinical course deteriorates. If IL-6 analysis was abnormal at entry point, we repeated on every 72 h as follow-up to assess severity, progression of illness and also titer level utilized to assess response to medical treatment. Follow-up HRCT thorax was done after 12 weeks or 3 months of discharge from hospital for analysis of post-COVID lung fibrosis in selected cases with abnormal IL-6 level at discharge and required bilevel positive airway pressure/noninvasive ventilation (BIPAP/NIV) during hospitalization and cases required oxygen supplementation at home [Figure 1].

Methodology of interleukin-6 titer assessment

Immunoturbidimetry.

Normal values

Normal values were up to <7 pg/mL.

Interpretation of results

1. Negative: Value up to <7 pg/mL[13]
2. Positive: Value above >7 pg/mL[13]
3. Significant: Four-fold raised IL-6 vale, i.e., >28 pg/mL
4. Highly significant: Sixteen-fold raised values, i.e., 98 pg/mL, i.e., level considered as required for labeled as cytokine storm
5. Follow-up significance: Values raised or decreased in two-to-four-fold change.

Statistical analysis

The statistical analysis was done using Chi-square test in R-3.4 is available as a Free Software under the terms of the (Free Software Foundation's GNU General Public License in source code form, Vienna, Austria). Significant values of Chi-square were seen from the probability table for different degree of freedom required. *P* value was considered significant if it was below 0.05 and highly significant in case if it was <0.001.

RESULTS: COVARIATES

In the present study, 2000 COVID-19 pneumonia cases were confirmed by COVID-19 RT-PCR, males were 1300/2000 and females were 700/2000, age >50 were 1200 cases, and age <50 were 800 cases. Significant association in IL-6 and COVID-19 pneumonia has been documented with variables such as age, gender, diabetes mellitus, IHD, hypertension, chronic obstructive pulmonary disease (COPD), and oobesity ($P < 0.00001$) [Table 1].

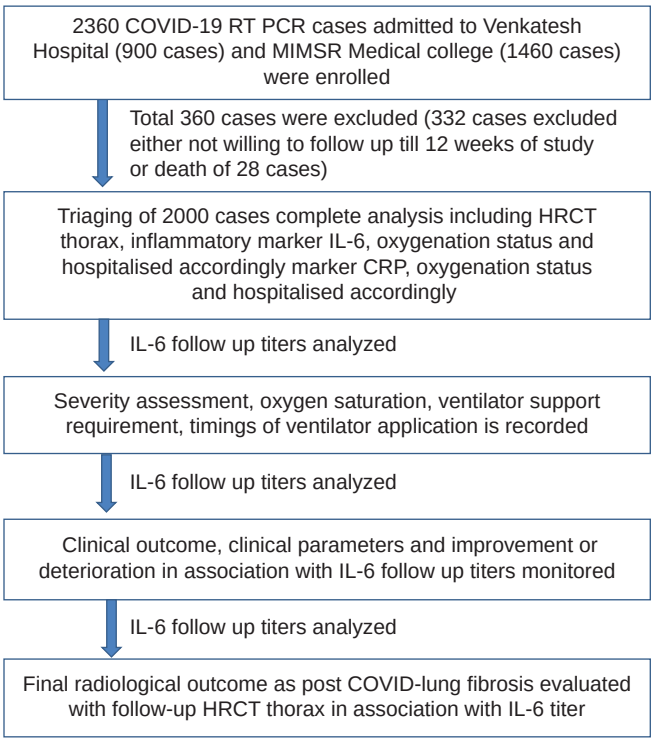

Figure 1: Flow of the study

Table 1: Other variables and interleukin 6 level in corona virus disease-19 pneumonia cases (*n*=2000)

COVID-19 RT PCR positive (*n*=2000)	IL-6 level normal (*n*=640)	IL-6 level abnormal (*n*=1360)	Chi-square test value and *P*
Age >50 years (*n*=1200)	280	920	χ^2=51.77
Age <50 years (*n*=800)	360	440	*P*<0.00001
Male gender (*n*=1300)	380	920	χ^2=6.5
Female gender (*n*=700)	260	440	*P*<0.0100
Diabetes mellitus (*n*=1200)	300	900	χ^2=33.77
Without diabetes (*n*=800)	340	460	*P*<0.00001
Hypertension (*n*=420)	320	100	χ^2=238.55
Without hypertension (*n*=1580)	320	1260	*P*<0.00001
COPD (*n*=300)	200	100	χ^2=97.46
Without COPD (*n*=1700)	440	1260	*P*<0.00001
IHD (*n*=400)	220	180	χ^2=60.77
Without IHD (*n*=1600)	420	1180	*P*<0.00001
Obesity (*n*=320)	40	280	χ^2=33.28
Without obesity (*n*=1680)	600	1080	*P*<0.00001

COVID-19: Corona virus disease-19, RT PCR: Reverse transcription polymerase chain reaction, IL-6: Interleukin 6, COPD: Chronic obstructive pulmonary disease, IHD: Ischemic heart disease

Results: Core observations

HRCT severity score at entry point with IL-6 level has significant correlation in COVID-19 pneumonia cases ($P < 0.00001$) [Table 2] IL-6 level has significant association with duration of illness (DOI) in COVID-19 pneumonia cases ($P < 0.00001$) [Table 3]. IL-6 level has significant association with SpO2 in COVID-19 pneumonia cases ($P < 0.00001$) [Table 4]. BIPAP/NIV requirement during the course of COVID-19 pneumonia in critical care setting has significant association with IL-6 level ($P < 0.00001$) [Table 5]. Timing of BIPAP/NIV requirement during course of COVID-19 pneumonia in critical care setting has significant association with IL-6 level ($P < 0.00001$) [Table 6]. Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in post-COVID lung fibrosis ($P < 0.00001$) [Table 7]. Follow-up IL-6 titer during hospitalization as compared to entry point normal IL-6 has significant association in post-COVID lung fibrosis ($P < 0.00001$) [Table 8]. Follow-up IL-6 titer during hospitalization as compared to entry point abnormal IL-6 has significant association in predicting cytokine storm irrespective normal or abnormal of IL-6 at entry point ($P < 0.0001$) [Table 9].

Table 2: Correlation of high resolution computerised tomography severity (at entry point) and interleukin 6 in corona virus disease-19 cases (*n*=2000)

HRCT severity	IL-6 level normal (*n*=640)	IL-6 level abnormal (*n*=1360)	Analysis
<8 score (*n*=600)	380	220	χ^2=224.87
9-15 (*n*=600)	180	420	*P*<0.00001
>15 (*n*=800)	80	720	

HRCT: High resolution computerised tomography, IL-6: Interleukin 6

Table 3: Duration of illness at entry point during hospitalization and interleukin 6 level in corona virus disease-19 pneumonia cases (*n*=2000)

DOI (days)	IL-6 level normal (*n*=640)	IL-6 level abnormal (*n*=1360)	Analysis
<7 (*n*=680)	60	620	χ^2= 185.65
8-15 (*n*=920)	320	600	*P*<0.00001
>15 (*n*=400)	260	140	

DOI: Duration of illness, IL-6: Interleukin 6

Table 4: Oxygen saturation at entry point and interleukin 6 level in corona virus disease-19 pneumonia cases (*n*=2000)

Oxygen saturation (%)	IL-6 level normal (*n*=640)	IL-6 level abnormal (*n*=1360)	Analysis
>90 (*n*=420)	220	200	χ^2=60.37
75-90 (*n*=980)	300	680	*P*<0.00001
<75 (*n*=600)	120	480	

IL-6: Interleukin 6

Table 5: Correlation of bilevel positive airway pressure use with interleukin 6 level in corona virus disease-19 pneumonia cases (*n*=2000)

BIPAP/NIV	IL-6 level normal (*n*=640)	IL-6 level abnormal (*n*=1360)	Analysis
BIPAP/NIV required (*n*=1200)	310	890	χ^2=26.21
BIPAP/NIV not required (*n*=800)	330	470	*P*<0.00001

BIPAP: Bilevel positive airway pressure, NIV: Noninvasive ventilation, IL-6: Interleukin 6

Table 6: Bilevel positive airway pressure/noninvasive ventilation initiation time at entry point and interleukin 6 level corona virus disease-19 pneumonia cases (*n*=1200)

BIPAP used (*n*=1200) with DOI	Abnormal IL-6 titer (*n*=580)	Four-fold IL-6 raised titer (*n*=620)	Analysis
Entry point <1 day (*n*=360)	220	140	χ^2=31.30
3-7 days (*n*=620)	300	320	*P*<0.00001
After 7 days (*n*=220)	60	160	

BIPAP: Bilevel positive airway pressure, IL-6: Interleukin 6, DOI: Duration of illness

DISCUSSION

Correlation of computed tomography severity (at entry point) and interleukin-6 in Coronavirus disease-19 cases

We have observed that CT severity can be considered the best visual marker of the severity of COVID-19 pneumonia which can be correlated with inflammatory markers such as IL-6, ferritin, CRP, LDH, D-Dimer and lymphopenia, lymphocyte platelet ratio. In the present study, the CT severity score at entry point with D-Dimer level has a significant correlation with COVID-19 pneumonia cases. ($P < 0.00001$) COVID-19 cases with CT severity score <8, 8–15 and >15 documented normal and abnormal IL-6 level in 380/220, 180/420 and 80/720 respectively of total of 1000 study cases we have also documented that CT severity assessment will guide in triaging cases in casualty and targeting interventions in indoor units accordingly to have successful treatment outcome. Various Authors[14-29] documented that IL-6 and other inflammatory markers as CRP, ferritin, and LDH has been correlated with CT severity and cases from mild to moderate to severe were having increasing trends of inflammatory markers.

Duration of illness at entry point during hospitalization and interleukin-6 level in corona virus disease-19 pneumonia cases (*n* = 2000)

In the present study, IL-6 level has a significant association with DOI in COVID-19 pneumonia cases. ($P < 0.00001$) COVID-19 cases with DOI <7 days, 8–15 days, and >15 days of onset of symptoms documented normal and abnormal IL-6 levels in 60/620, 320/600, and 260/140 cases respectively. We have documented proportionate number of COVID-19 pneumonia cases with DOI <7 days and many cases with DOI >15 days were having normal IL-6 level, while cases between 7 and 14 days of DOI were having

Table 7: Abnormal interleukin 6 level at entry point (*n*=1360) and follow up and its correlation with post-corona virus disease-19 lung fibrosis

Post-COVID pneumonia fibrosis	IL-6 titer increased/ abnormal at entry point (*n*=800)	IL-6 titer fourfold increased during follow up (*n*=560)	Analysis
Pulmonary fibrosis present (*n*=420)	80	340	χ^2=198.45 *P*<0.00001
Pulmonary fibrosis absent (*n*=940)	720	220	

COVID-19: Corona virus disease-19, IL-6: Interleukin 6

Table 8: Normal interleukin 6 level (*n*=640) at entry point and follow up and its correlation with post-corona virus disease-19 lung fibrosis

Post-COVID pneumonia fibrosis	IL-6 normal at entry point and remained less than fourfold (*n*=240)	IL-6 titer fourfold increased during follow up (*n*=400)	Analysis
Pulmonary fibrosis present (*n*=80)	10	70	χ^2=12.19 *P*<0.00048
Pulmonary fibrosis absent (*n*=560)	230	330	

COVID-19: Corona virus disease-19, IL-6: Interleukin 6

Table 9: Normal interleukin 6 level (*n*=640) and abnormal interleukin 6 level at entry point (*n*=1360) and its correlation with follow up titer with cytokine storm (*n*=392)

Cytokine storm	Normal IL-6 titer at entry point (*n*=640)	Abnormal IL-6 at entry point (*n*=1360)	Analysis
Cytokine storm present (*n*=392)	80	312	χ^2=15.05
Cytokine storm absent (*n*=1608)	560	1048	*P*<0.0001

IL-6: Interleukin 6

abnormal or raised IL-6 level. Rational for observation is not known, may be inflammatory pattern is different during 1st and 3rd weeks as compared to 2nd week of illness. We have also correlated IL-6 pattern with other inflammatory markers such as Ferritin, CRP, and LDH and documented that these markers raised parallel to IL-6. Raised IL-6 after 2nd week of illness may indicate worsening of COVID-19 pneumonia or secondary bacterial infection which will guide intensivist to screen for infection and formulate antibiotics policy accordingly. Thus, follow-up titers will guide indirectly in protocolized management in critical care settings.

Correlation of bilevel positive airway pressure/ noninvasive ventilation use with interleukin-6 level in coronavirus disease-19 pneumonia cases (*n* = 2000)

In the present study, BIPAP/NIV requirement during the course of COVID-19 pneumonia in critical care setting has a significant association with IL-6 level ($P < 0.00001$). COVID-19 cases received BIPAP/NIV during hospitalization were documented normal and abnormal IL-6 level in 310/890 and 330/470 cases. respectively. We have documented IL-6 level has positive correlation with requirement of BIPAP/NIV, high flow nasal canula (HFNC) oxygen supplementation, and invasive mechanical ventilation in critical care setting. Studies by various authors[30-33] have documented, high IL-6 is predictor of critical illness requiring intensive care unit treatment including noninvasive and invasive ventilatory support as compared to cases with normal IL-6 level.

Correlation of oxygen saturation at entry point and interleukin-6 level in corona virus disease-19 pneumonia cases (*n* = 2000)

In the present study, IL-6 level has a significant association with SpO2 in COVID-19 pneumonia cases. ($P < 0.00001$) COVID-19 cases with SpO2 >90%, 75%–90%, and <75% observed as normal and abnormal IL-6 level in 220/200, 300/680, and 120/480 cases, respectively. We have documented hypoxia at entry point during hospitalization has a positive correlation abnormal IL-6 level. Numerous authors[20-31,33-43] have documented that higher IL-6 level is associated with hypoxemia, also mentioned that higher IL-6 level is an indicator of advanced pneumonia process and progressed lung parenchymal inflammatory injury or necrosis resulting into failure of oxygenation.

Correlation of bilevel positive airway pressure/ noninvasive ventilation initiation time at entry point and interleukin-6 level coronavirus disease-19 pneumonia cases (*n* = 1200)

In the present study, the timing of BIPAP/NIV requirement during COVID-19 pneumonia in critical care setting has a significant association with IL-6 level ($P < 0.00001$). COVID-19 cases received BIPAP/NIV at entry point <1 day, 3–7 days, and after 7 days of hospitalization were documented significance in four-fold raised IL-6 level in 110/70, 150/160, and 30/80 cases. respectively. We have observed that early initiation of BIPAP/NIV in COVID-19 pneumonia cases meeting the criteria of oxygen supplementation, i.e., SpO2 <89% at room air during hospitalization were having beneficial effect in controlling systemic immune-inflammatory syndrome which can be measured by IL-6 level in follow-up. Rational for similar observation may be because of improvement in oxygenation and lung compliance after the use of BIPAP/NIV in these cases. A plausible mechanism is that hypoxia is important trigger for rise in inflammatory markers by means of rise in hypoxia-inducible transcription factor. Previously published studies by various authors[34-37] have documented similar observations to our study and noted a higher level of IL-6 titer in those cases that required ventilatory support during hospitalization in intensive care units.

Normal interleukin-6 level (*n* = 640) and Abnormal interleukin-6 level at the entry point (*n* = 1360) and its correlation with follow-up titer with cytokine storm (*n* = 392)

In the present study, we have observed that entry point normal and abnormal IL-6 titer has a significant association with cytokine storm ($P < 0.00001$). Total COVID-19 cases with cytokine storm have normal 80/392 and abnormal 312/392 IL-6 titer. Total COVID-19 cases without cytokine storm have 560/1608 and 1048/1608 have entry point abnormal IL-6 titer. We have also documented that "Cytokine storm" is independent predictor of poor outcome and many of these cases represent rapidly evolving COVID-19 pneumonia progressing to ARDS and requiring ventilatory support. We have followed all these cases with cytokine storm and observed that proportionately large number of these cases were required high-flow oxygen supplementation for a longer duration during hospitalization and few cases require oxygen supplementation at home for 3 months after discharge form critical care setting. Numerous Authors[16-29] have documented similar observation to our study. We have documented the significant role of tocilizumab in curtailing "cytokine storm" with severe COVID-19 pneumonia cases requiring ventilatory support and it will show improvement in oxygenation, inflammatory markers titer, ventilatory support requirement in majority of cases, and mortality benefit in few cases. Thus, timely IL-6 inhibitor or tocilizumab has outcome modifying role in intensive care units in cases with ALI/ARDS with IL-6 level above 100 pg/ml. Various authors[24-28,39-43] have documented similar to our findings in their studies and mentioned that IL-6-targeted treatment will help in disease progression and good treatment outcome.

Other important observation in this study

Correlation of Abnormal interleukin-6 level at entry point (n = 1360) and follow-up and its correlation with post-COVID lung fibrosis

In the present study, the radiological outcome as post-COVID lung fibrosis has significant association with four-fold rise in followup IL-6 titer during hospitalization in cases with abnormal IL-6 titer at the entry point ($P < 0.00001$). Total 80/420 and 340/420 Post-COVID-19 lung fibrosis cases were having abnormal and four-fold rise in IL-6 titer, respectively. Total 720/940 and 220/940 COVID-19 cases were having no radiological sequelae with abnormal and four-fold rise in IL-6 titer, respectively. We have documented that serial measurement of IL-6 during hospitalization irrespective of entry point abnormal level has a very well correlation with the requirement of interventions in indoor and intensive care units as HFNC, BIPAP/NIV, and invasive mechanical ventilation. Cases with cytokine storm were picked up earlier by serial IL-6 level and proportionately large number will have post-COVID lung fibrosis. Thus, IL-6 will indirectly help in predicting future risk of the development of post-COVID lung fibrosis. Authors[26-32,39-43] have observed similar findings in their respective studies and reported rising titers of IL-6 is marker of exaggerated lung inflammation and necrosis which will result in lung fibrosis.

Correlation of Normal interleukin-6 level (n = 640) at entry point and follow-up and its correlation with post-COVID lung fibrosis

In the present study, radiological outcome as post-COVID lung fibrosis has a significant association with four-fold rise in follow-up IL-6 titer during hospitalization in cases with normal or less than four-fold IL-6 titer at entry point ($P < 0.00001$). Total 10/80 and 70/80 post-COVID lung fibrosis cases were having normal or less than four-fold IL-6 titer at entry point and sequential four-fold rise in IL-6 titer respectively. Total 230/560 and 330/560 cases were having no radiological sequelae with normal or less than four-fold IL-6 titer at entry point and serial four-fold rise in IL-6 titer, respectively. We have documented that, normal IL-6 is predictor of good clinical and radiological outcome and serial measurement of IL-6 during hospitalization irrespective of entry point level has very well correlation with underlying lung pathology. We have observed that IL-6 rising trends would help in predicting exaggerated underlying lung parenchymal damage secondary to cytokine-induced lung necrosis and cytokine-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). These insults as necrosis or ALI/ARDS are considered early marker of future lung fibrosis. Authors[29-39] documented similar observation and mentioned importance of serial IL-6 titers in assessing high-risk cases for respiratory failure. They have observed the role of follow-up IL-6 titers in assessing critical COVID-19 cases and crucial role in de-escalating interventions in intensive care unit along with clinical assessment. Authors have documented rising trends of IL-6 is marker of post-COVID lung fibrosis.

Correlation of other variables and interleukin-6 level in corona virus disease-19 pneumonia cases

We have documented that the age and gender of included cases have significant association with IL-6 level. Studies by various authors[16-26,33-43] also documented similar observations. In present study, comorbidity such as diabetes mellitus, COPD, Hypertension, IHD, and obesity has significant association IL-6 level ($P < 0.00001$). Studies by various authors[16-26,33-43] also documented similar observations in IL-6 level and its correlation with underlying comorbidities.

Limitations of study

Our study is having enough sample size and analyzing the role of IL-6 at entry point and follow-up during the 12 weeks and association with post-COVID-19 lung fibrosis is documented. First limitation is confounding factors leading to abnormal IL-6 titer in other infective, inflammatory, and rheumatological disorders were not done during the entire duration of 12 weeks and its effect on COVID-19 severity parameters was not possible. Second limitation is the association of IL-6 titer with other modes of intensive care treatments as high flow nasal cannula and invasive mechanical ventilatory support is not assessed differently and cases predominantly on BIPAP/NIV were considered as ventilatory support, probably because majority of COVID-19 cases receiving high flow nasal cannula were shifted to BIPAP/NIV and or mechanical ventilation in intensive care units.

Implications to clinical practice and implications to future research

The role of IL-6 in COVID-19 pandemic has studied widely during all three waves with variants such as Wuhan, delta and omicron. In each wave, IL-6 has documented role in predicting severity, course during hospitalization, guided interventions requirement in indoor setting, and helped in analyzing final outcome. The role of sequential IL-6 titers in predicting deadly cytokine storm has been evaluated globally and IL-6 guided therapy has documented effects on outcome in COVID-19 pneumonia. We recommend further evaluation and more global research:

1. Although cytokine storm has been documented in rheumatological conditions is similar to COVID-19 pneumonia, outcome and response to therapy is different
2. Cytokine storm was common in all variants of COVID-19, but presentation was different and manifested as pulmonary type in delta variant, pulmonary plus extrapulmonary on Wuhan variant, and predominant extrapulmonary type in the omicron variant. Rational for these findings mandates more workup
3. Cytokine storm and IL-6 surge were documented in selected cases of COVID-19. IL-6 titer required for labeling cytokine storm is validated. Discordance between IL-6 titer and cytokine storm has documented in all three waves of COVID-19. Many patients with less than four-fold rise in titer were having cytokine storm-like presentation while few cases with more than sixteen-fold rise in titer were not having symptoms of cytokine storm. Rational for similar observations needs more research
4. Rational for disproportionate surge of IL-6 as per genetic makeup of virus is issue of real research. Finally, patients' characteristics or high-risk indictors for cytokine storm or IL-6 surge need further research.

CONCLUSIONS

IL-6 is an easily available, sensitive, reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pneumonia. IL-6 has a very crucial role in COVID-19 pneumonia in predicting severity of illness, especially "follow up titers" have a significant role in step-up or step-down interventions in critical care settings. Correlating IL-6 with variables such as DOI, oxygenation status and timing of BIPAP/NIV has an important role in predicting outcome.

IL-6 titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial IL-6 has progressed to critical course and we have documented follow up titers has played crucial role with other inflammatory markers, and many times in 2nd week of illness rising titers indicates exaggerated ongoing inflammation and worsening of pneumonia which will help to target therapy accordingly. IL-6 follow-up titer can help in predicting progression of COVID-19 pneumonia, and assessing risk of post-COVID lung fibrosis.

Sequential IL-6 titer during follow-up has a crucial role in predicting course during hospitalization and guided treatment in these cases with high risk of progression of COVID-19 pneumonia. We have documented a proportionate number of mild COVID-19 cases as per CT Severity with initial normal IL-6 has progressed to critical illness during the 2nd week of hospitalization and these cases were earliest picked up by follow-up IL-6 titers with other inflammatory markers. We recommend follow up titers in all hospitalized cases which will guide timely interventions with successful treatment outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Management of foreign body ingestion in pediatric population: A single-center study

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Abstract

Background: Children of all ages may ingest a foreign body (FB). Most (>95%) of ingestions are accidental. Gastrointestinal tract obstruction or impaction by a FB depends on the physical properties of the object such as size, shape, and composition. The majority of ingested FBs are low-risk objects and can be managed without imaging or intervention where as high-risk objects and symptomatic children may require careful observation and surgical intervention. The aim of our study is to discuss our experience of management of FB ingestion in children in IPGME&R and SSKM Hospital, a tertiary care centre and to identify the high-risk FBs ingested and discuss the symptoms where conservative managements can be done even in sharp objects.

Materials and Methods: This observational single institute-based study was conducted in the Department of Pediatric Surgery in IPGME&R and SSKM Hospital and data were collected and analyzed statistically.

Results: A total of 84 patients came with ingested FBs (Boy – 59 and Girl – 29) and 22 were sharp FBs. Among nonsharp FBs, coins are most common 40 (47.6% of all FBs). Most of them were asymptomatic 75 (89.3%) and among all four required surgical intervention and eight were removed by endoscopy. In 72 patients, no intervention was required for FB ingestion including 16 sharp objects.

Conclusion: Most of the ingested FBs are expelled through stool spontaneously. Nonsharp FBs such as magnets and button battery large size are high-risk objects and require active surgical intervention and sharp FBs need very much careful observation after admission and very few requires surgical intervention. Endoscopic removal is indicated in some early cases.

Keywords: Magnet ingestion, needle ingestion, open safety pin in the abdomen, sharp foreign body

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INTRODUCTION

Foreign body (FB) ingestion is very common among pediatric population. Children of all ages may ingest a FB; however, the highest incidence is between the ages of 6 months and 3 years, and in those with developmental or behavioral problems. Most (>95%) of ingestions are accidental.[1-3] Few older children with underlying psychiatric problems may intentionally ingest FBs.[2,3] An estimated 40% of FB ingestions in children are unwitnessed, and in many cases, the child never develops symptoms.[4,5] Gastrointestinal (GI) tract obstruction or impaction by a FB depends on the physical properties of the object, including its size, shape and composition.[6,7] The majority of ingested FBs are low-risk objects and can be managed without imaging or intervention. Button batteries and magnets are high-risk objects and require

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imaging.[8] Large-sized objects and objects impacted in the oropharynx require surgical review.[6,7,9,10] In this study, we will discuss our experience of management of FB ingestion in children in IPGME&R and SSKM Hospital, a tertiary care centre for pediatric surgery and aim of our study is to identify the high-risk FBs ingested and discuss the symptoms where conservative managements can be done even in sharp objects and to analyze surgical as well as endoscopic guideline for the treatment of FB Ingestion in children in the light of recent advances.

MATERIALS AND METHODS

This observational single institute-based study was conducted in the Department of Pediatric Surgery in IPGME&R and SSKM Hospital during February 2021 to September 2022. Data were collected from emergency register (trauma care centre), outpatient department (OPD) register (pediatric surgery), OT registers (main OT complex and trauma care OT), and bed-head tickets. All patients with ingested FB were included in the study. Patients with FB stuck in nasopharyngs, laryngopharyngs, trachea or bronchial tree or patients with FB after Blunt trauma (chest, abdomen, etc.), and blast injury or road traffic accidents or entry of FB by any other route were not included in the study.

After initial assessment by history (witnessed or unwitnessed, duration, previous history of FB ingestion, developmental history, previous gastrointestinal (GI) surgery or other GI abnormalities etc), and clinical examination (symptomatic or asymptomatic) screening radiology assessments (X-ray chest and abdomen, anteroposterior and/or lateral view) were done. Patients are then advised either follow-up in OPD or indoor admission for observation or intervention (endoscopic removal or open surgical procedures) according to nature of problem. Data were tabulated and collected for analysis.

RESULTS ANALYSIS

In our study, we collected data from total 84 patients during this study period among them 59 were boys and 25 girls [Table 1].

Minimum age of presentation was 9 months (girl) and maximum 11 years (boy). In our study, there was nine infants and 85.7% ($n = 72$) patients were under 4 years of age [Table 2].

Among all children with FB ingestion, nine patients were symptomatic (10.7%) and 75 (89.3%) asymptomatic. Their symptoms varied from minimal epigastric discomfort to abdominal distension and vomiting with features of peritonitis (magnet as FB) [Table 3].

Among 62 nonsharp, FBs we found coin, (40) shirt button (9), button battery (6), magnet-1 (6 in number), locket (1), marble (5) and were found 22 sharp FBs with needle (4), nail (5), screw (2), and safety pin (open 6 and closed 5). Sixteen passed spontaneously after careful observation. Six patients required intervention, three were removed endoscopically, and three required surgical exploration [Tables 1 and 3].

Forty patients found with FB coin and all of them passed through stool spontaneously and about 90% passed within 1 week. We also could find six children coming with small (<20 mm) button battery ingestion. All were removed spontaneously through stool within 5 days after ingestion. Among nonsharp FBs, three boys and two girls required endoscopic removal and one boy needed surgical intervention (magnet as FB) [Table 1].

Table 1: Study population distribution table

	Boys	Girls
Nonsharp (62)	Conservative-41	Conservative-15
Boys-45	Endoscopic-3	Endoscopic-2
Girls-17	Surgical-1	Surgical-0
Sharp-22	Conservative-10	Conservative-6
Boys-14	Endoscopic-2	Endoscopic-1
Girls-8	Surgical-2	Surgical-1
Total	59	25

Table 2: Age distribution table

Age (years)	Children with FB ingestion (%)
<1	9 (10.8)
1-<2	24 (28.6)
2-<3	21 (25)
3-<4	18 (21.4)
4-<6	6 (7.2)
6-<8	4 (4.8)
8-<10	1 (1.1)
10-<12	1 (1.1)

FB: Foreign body

Table 3: Types of foreign body ingestion and symptoms after ingestion

Nature of FB	Type of FB	Symptoms
Nonsharp (62)	Coin-40 Shirt button-9 Button battery-6 Magnet-1 (6 in number) Locket-1 Marble stone-5	Total-7 Minimum epigastric discomfort, pain abdomen (coin) Abdominal discomfort with vomiting (magnet)
Sharp (22)	Needle-4 Safety pin (open)-6 Safety pin (closed)-5 Nail-5 Screw-2	Total-2 Pain abdomen (needle and safety pin)

FB: Foreign body

Among sharp FBs, four children presented with FB ingestion of needle and all required intervention-1 was removed endoscopically and the rest all three needed exploratory laparotomy. We also followed five patients with nail and two with screw which also required no active intervention. We also found 11 cases of safety pin among which four were open. Except one open safety pin which was removed endoscopically, all could pass through stool spontaneously [Tables 1 and 3].

In our study, 72 children passed FB through stool spontaneously, endoscopic removal was done in only 8 (9.5%) patients and four required surgical intervention, one with magnet ingestion, and other three with needle ingestion [Table 4].

DISCUSSION

FB ingestion in children is very common and they are mostly not witnessed and asymptomatic. Almost three-fourths of children presenting with FB ingestion are within 4 years of age and >95% of them are accidental.[1-3] Few older children with developmental or behavioral problems or underlying psychiatric problems may intentionally ingest FBs. In our study in a tertiary care center emergency department and OPD, we collected data from total 84 patients during this study period among them 59 boys and 25 girls. We could not find any behavioral or gross developmental problems among any of them. Minimum age of presentation was 9 months girl and maximum 11 years boy 85.7% (n = 72) were under 4 years age.

Very few children with FB ingestion are symptomatic at early stage when they are stuck in upper digestive track. Symptoms of GI tract obstruction by a FB depend on the physical properties of the object, including its size, shape, and composition and anatomical location of impaction[6,7,9,10] [Table 5]. In our study, nine patients were symptomatic (10.7%) and 75 (89.3%) asymptomatic. Their symptoms varied from minimal epigastric discomfort to abdominal distension and vomiting with features of peritonitis.

Ingested FBs are mostly found in the domestic environment and are low-risk objects and can be managed without imaging or intervention. In 80%–90% of cases, the FB passes without complications and is evacuated with faeces within a few days, and 10%–20% of cases may require endoscopic removal because the FB does not pass easily or because it is potentially harmful. Less than1% may require surgery.[11-13] In our study, 72 children passed FB through stool spontaneously, eight FBs were removed by endoscopy and four required surgical intervention.

Coin

Coins are the most commonly ingested FB in children.[14] In our study, we found 40 patients as FB coin which is almost half of all FBs ingested. All of them passed through stool spontaneously and about 90% passed within 1 week. Sometimes FBs could have found in stool and most of the time unnoticed. Symptomatic children presenting with airway obstruction, drooling, vomiting, chest discomfort, or pain warrant emergency endoscopic removal. Conners *et al.* suggested that 60% of coins lodged in the lower esophagus have been observed to pass spontaneously.[15] Once coins are observed to successfully pass through the esophagus, they are likely to progress and pass spontaneously.[16-18] Serial X-rays should be obtained every 1 or 2 weeks until passage of the coin has been confirmed [Figure 1].

Button battery

We could found six children coming with small (<20 mm) button battery ingestion. All were removed spontaneously through stool. Button batteries are potential risk elements for causing local chemical and electrical (lithium battery)-induced local mucosal damage. Usually, small

Table 4: Surgical procedures performed in patients

Patient	Location	FB	Symptoms	Surgery
3 years/ boy	Small intestine (ileum)	Multiple magnets	Presented after 2 days abdominal discomfort, vomiting, pain abdomen X-ray shows beaded ROS near right lower quadrant, no features of intestinal obstruction	Exploratory laparotomy, two bowel loops adhered, trapped mesentry in between, and bowel walls perforated d/t approximation of magnets, resection anastomosis done
4 years/ boy	Ileum	Needle	Presented after 2 days, was following up with serial X-rays, nonprogression of ROS at right lower abdomen, asymptomatic	Exploratory laparotomy, FB (needle) was stuck in ileum wall, and was removed by enterotomy, primary repair done of enterotomy
2 years/ boy	Meckle's diverticulum	Needle	Asymptomatic Nonprogression of ROS at middle of the abdomen	Exploratory laparotomy, FB stuck in meckle's divrerticulum, removed and resection anastomosis of diverticulum done
3 years/ girl	Ileum	Needle	Asymptomatic Nonprogression of ROS at right lower abdomen	Exploratory laparotomy FB stuck in ileum enterotomy, and removed

FB: Foreign body, ROS : Radio opaque shadow

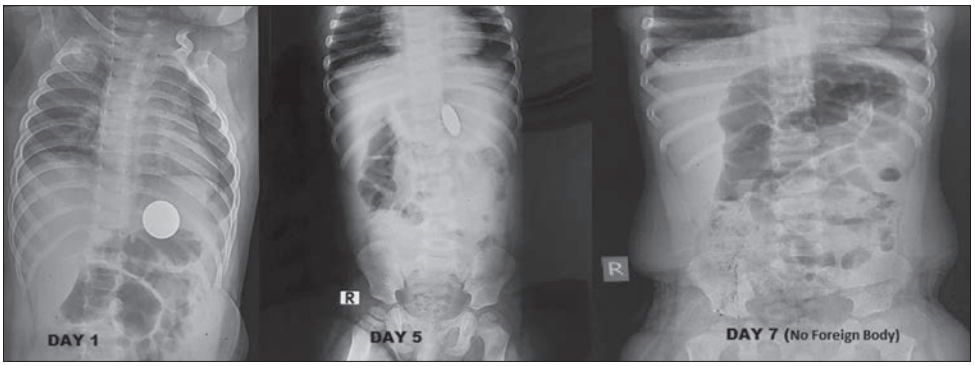

Figure 1: Serial X-rays showing change of positions of FB (coin) and spontaneous expulsion. FB: Foreign body

Table 5: Symptoms of foreign body impaction after ingestion

Location of FB	Symptoms
Esophagus	Dysphagia, sialorrhea, cough, hematemesis, globus sensation, thoracic cluttered sensation, or respiratory symptoms due to the compressive effect on the trachea
Stomach	Typically asymptomatic, although large objects may cause pyloric obstruction and cause vomiting and/or refusal to feed
Intestine	Usually asymptomatic; ileocecal valve retention rarely occurs, with possible complications such as obstruction, perforation and peritonitis

FB: Foreign body

button batteries (diameter ≤20 mm) do not cause serious complications that are observed in association with larger button batteries (diameter ≥20 mm).[19] Once they are past the duodenal sweep, 85% of button batteries pass in <72 h.[20] In our study, all (batteries) passed through stool within 5 days.

Magnet

In recent times, technologically advanced toys in the household have resulted in an increased exposure to higher voltage batteries and powerful magnets that carry a high incidence of morbidity and mortality when accidentally ingested by children.[8] We encountered one patient with ingestion of FB as magnet and it was multiple in number (6). Presentation was at day 2 being referred from another hospital. After radiology and clinical features of abdominal distension and vomiting, we planned for exploration immediately and found two bowel loops adhered and trapped mesentery in between bowel loops and bowel walls were perforated due to approximation of magnets. Resection anastomosis was done [Figure 2]. We could save the patient by laparotomy and now following up in OPD. According to the literature, single small magnet is expected to be passed spontaneously. If multiple magnets or a single magnet with a metallic FB has been ingested, the contact between the mucosal surfaces of different body parts can cause mucosal pressure necrosis, as well as intestinal obstruction, fistula, and/or perforation; therefore, surgical removal is needed in such cases.[21-23]

Needle, nail, and screw

A total of 22 patients attended emergency with sharp FB ingestion and among them needle (4), nail (5), screw (2), and safety pin (open 6 and closed 5) were found. Sixteen passed spontaneously after careful observation. Six patients required intervention, three were removed endoscopically and three required surgical exploration.

In our study, four patients presented with FB ingestion of needle and all required intervention. One was removed endoscopically and the rest all three needed exploratory laparotomy and was removed by enterotomy [Figure 3]. Literature says if a sharp FB has passed ligament of Treitz, i.e., reached jejunum surgical removal can be considered in symptomatic children. In asymptomatic patients, close clinical follow-up with serial X-rays obtained after admitting the patient are recommended. The mean GI transit time for FBs in children is approximately 3.6 days.[24] So after 4 days, if the FB does not show the expected passage, a bowel perforation or a congenital anomaly is suspected, and surgical removal of the FB needs to be considered.[25-27] We also followed five patients with nail and two with screw which was followed up with close observation after admission with serial X-rays [Figure 4] and were expelled through stool spontaneously within 6 days.

Safety pin

In our study, we encountered total 11 cases of safety pin among which four were open. Except one open safety pin which was removed endoscopically, all could pass through stool spontaneously [Figure 5]. We noticed that time taken to expel FB through stool is inversely proportional to age, i.e. older children could pass FB (open Safety pin) early. In our study age of 4 patients are 2, 3, 3.5 and 4 years and time taken to expel FB (open Safety Pin) through stool are 6, 5, 5 and 4 days after ingestion respectively.

May be large diameter and peristalsis of bowel fasten expulsion. Gün *et al.* showed in their study of 49 patients,

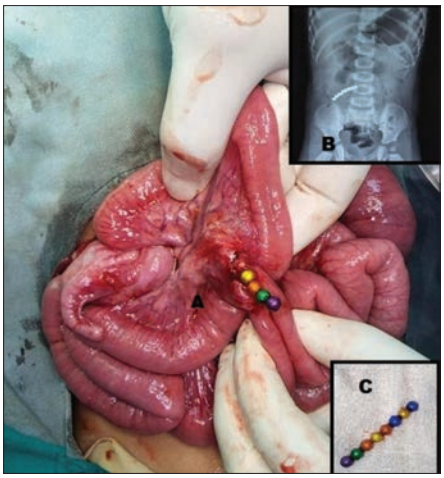

Figure 2: Magnets are being removed from adhered and perforated ileum (A), X-ray showing beaded foreign body (B) and magnet after removal (C)

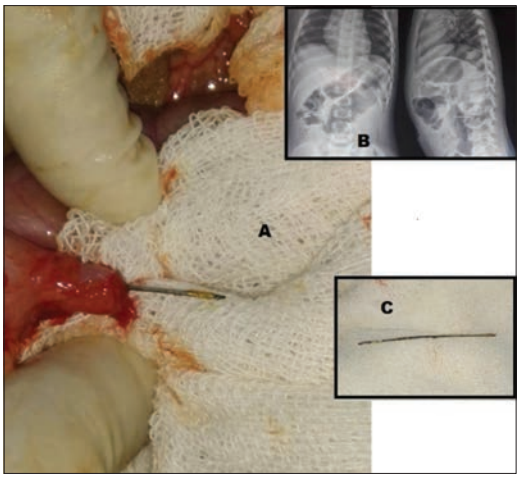

Figure 3: Removal of needle after enterotomy (A), Radiology showing ingested needle (B) with AP and lateral view and needle after removal (C)

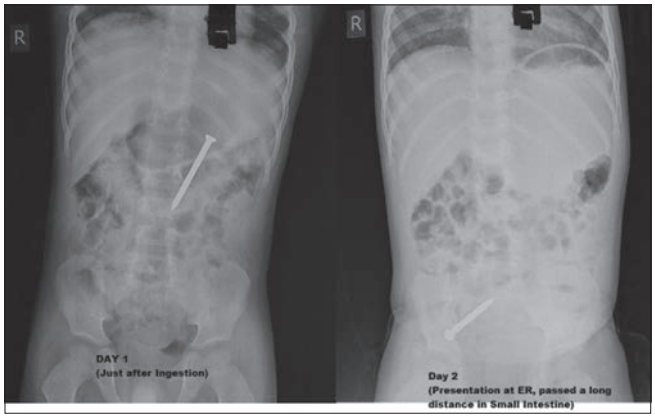

Figure 4: Serial X-ray of ingested FB (nail) shows gradual movement without symptoms. FB: Foreign body

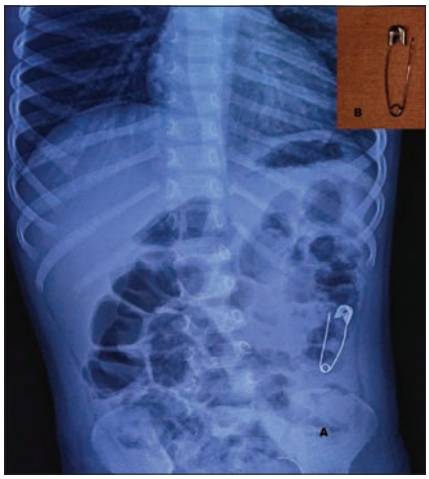

Figure 5: Ingested open safety pin (A), open safety pin after expulsion through stool (B)

seven required removal by endoscopy and seven by surgical exploration including one stuck at colon.[28] Carotid artery rupture,[29] hemopericardium and cardiac tamponade,[30] duodenocolic fistulas,[31] and incarcerated umbilical hernia[32] have also been reported as serious complications. Thus, the best option is to remove the safety pin using endoscopy while it is still in the esophagus and stomach following an Nothing per oral (NPO) status. In our study, we could remove FB by endoscopy, where safety pin was lodged in the 2nd part of duodenum.

In our study, endoscopic removal was done in only 8 (9.5%) patients. According to the literature, endoscopic removal of the FB is necessary in a small percentage of patients.[33,34] In symptomatic patients with a FB in the esophagus, removal is indicated within 2 h of presentation. In asymptomatic patients removal is, however, indicated if the FB has been stuck in the esophagus for more than 24 h (or for an unknown period). The recent guidelines of the European Society of Gastroenterology, Hepatology, and Pediatric Nutrition clearly describe the indications and timing of endoscopic surgery.[33,34]

Enteral management

Children after FB ingestion are advised normal diet to maintain normal bowel peristalsis when there is no features of obstruction. When high-risk FBs are ingested, NPO status is maintained for endoscopic or surgical intervention.

Outpatient department follow-up

Some children may repeat the incident. Parental monitoring is important and also to assess developmental and psychological status to be checked for and necessary counseling is mandate.

CONCLUSION

Management of FB in pediatric population depends on type and nature of FB and knowledge about its physical

nature and timing guides their treatment. Most of the ingested FBs are expelled through stool spontaneously. Nonsharp FBs such as magnets and button battery large size are high-risk objects and require active surgical intervention and sharp FBs need careful observation after admission and very few requires surgical intervention. Endoscopic removal is indicated in some early cases. It may be repeated in some child. Proper parental care is important. Laparoscopic removal of abdominal FB or removal without enterotomy (by appendectomy) is recent advances. In future studies, we are looking forward to focus on these.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Emphysematous pyelonephritis: An assessment of prognostic factors and the role of early pigtail drainage

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Abstract

Introduction: The management of emphysematous pyelonephritis (EPN), a necrotizing renal infection, has shifted from more invasive to less invasive approach in due course of time with decrease or reduction in mortality rate.
Aim: To analyze the clinical spectrum, prognostic factors, different management strategies, and the outcome of the patients of EPN with the role of early pigtail drainage.
Materials and Methods: The study was carried out at a tertiary care hospital from January 2016 to December 2021 and included patients who were diagnosed with EPN. The data on the demographic profile, clinical features, biochemical parameters, imaging studies, management, and outcome of patients of EPN were recorded.
Results: A total of 51 patients of EPN were studied and were divided into two groups, responders (40 patients) and nonresponders (11 patients), based on their clinical progression and outcome. Among responders and nonresponders, a significant difference was seen in terms of age, presentation of altered consciousness and shock, average hemoglobin, average serum creatinine, and presence of thrombocytopenia. Out of total 51 patients, 13 (25.49%) showed a response with antibiotics only, DJ stenting was done in five (9.8%) patients, and pigtail catheterization in 33(64.7%) patients. There was a significant difference seen in the response with early pigtail drainage. Nephrectomy was needed in eight (15.68%) patients, and the mortality rate was 9.8%, with the death of five patients.
Conclusion: Advanced age, lower hemoglobin levels, thrombocytopenia, raised serum creatinine levels, altered mental status, and presence of shock can be used as a score for poor prognosis. With the use of broad-spectrum antibiotics and early pigtail drainage, a large number of patients with EPN can be managed effectively. Nephrectomy should be reserved for patients who fail to respond to conservative management or those with advanced disease with the presence of multiple risk factors.

Keywords: Emphysematous pyelonephritis, pigtail drainage, prognostic factors

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INTRODUCTION

Emphysematous pyelonephritis (EPN) is an acute, life-threatening, necrotizing infection of the kidney characterized by the accumulation of gas in the renal parenchyma and within the surrounding tissues.[1]This condition was first described by Kelly and Mac-Cullem,[2]

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who reported a case of gas-forming necrotizing renal infection with pneumaturia. However, the term EPN was first used by Schultz and Klorfein.[3] There is a known female preponderance among EPN patients, and 90% of patients of EPN have associated diabetes.[4,5] EPN can also be seen in debilitated immune-deficient individuals or patients having obstructed urinary systems with infective nidus.[6,7]Association with urinary tract obstruction is seen in 20% of the patients.[8]The etiology of EPN is multifactorial, with the main factors being gas-forming bacteria, renal vascular compromise, high tissue glucose level, and a defective immune response.[9]The causative organisms involved are *Escherichia coli*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Clostridium*, *Streptococcus*, *Candida*, *Aspergillus*, and *Cryptococcus* species with *E. coli* being the most commonly encountered organism; however, a polymicrobial infection is not uncommon.[10,11]Though EPN is a rare condition but it requires early diagnosis and management due to associated mortality. Management varies from a conservative approach, including vigorous resuscitation, antibiotic treatment, and glycaemic control, to aggressive surgical intervention-like nephrectomy in refractory cases.

MATERIALS AND METHODS

The study was an ambispective observational study carried out by the Department of Urology, Nephrology and Endocrinology at a tertiary care hospital from January 2016 to December 2021. From January 2016 to December 2019, all the medical records of the patients who were diagnosed with EPN were retrospectively analyzed, and from January 2020 to December 2021, a prospective analysis of all the patients who were admitted with the diagnosis of EPN was done, and the patients were managed as per standard protocols. Ethical approval was taken from the institutional ethical committee. All the patients included in the study had evidence of gas in renal collecting system, parenchyma, or surrounding tissue on computed tomography (CT) scan. Patients with other possible causes of gas in the renal system as those having fistulous communication between the urinary system and bowel or any recent history of urinary tract instrumentation, trauma, urinary catheterization, or drainage, were excluded. Data on the demographic profile, clinical features, biochemical parameters, imaging studies, management, and outcome of patients were recorded. The baseline parameters included age, sex, and the presence of any comorbidities like diabetes or hypertension. The clinical features included symptoms at the time of presentation and physical findings like the hemodynamic status of the patient, the mental status of the patient, or the presence of any tenderness. The laboratory variables included hemoglobin levels, total leukocyte count, platelet count, blood sugar levels, serum creatinine level, and urine microscopy and culture. According to Huang and Tseng's classification, the patients were divided into four groups based on the extent of gas visible on the CT scan.[9] Class 1 patients had gas only in the collecting system, also known as emphysematous pyelitis. Patients in class 2 had gas only in the renal parenchyma without additional renal extension. Patients in class 3A had gas or an abscess extending into the perinephric space, while those in class 3B had gas or an abscess extending into the pararenal space. EPN in a solitary kidney or bilateral involvement was considered as class 4.

Patients were managed according to the severity of infection and associated comorbidities. Initial management included fluid and electrolyte management, aggressive sugar control, optimization of coagulation values, and antibiotic administration. Broad-spectrum antibiotics (intravenous piperacillin/tazobactam or meropenem) were used initially, which were changed to a specific antibiotic once the culture sensitivity report was available. Patients having obstructed urinary systems were immediately managed by a double J stent (DJ stent). In cases with significant dilatation of the pelvicalyceal system or any significant renal or extrarenal collection, percutaneous pigtail catheter placement was done under local anesthesia using ultrasonography (US) guidance. Nephrectomy was done in the patients who did not respond to the above therapies.

In this study, all the patients were divided into two groups, the "responders" and the "nonresponders," according to their outcomes. Patients who were successfully treated or showed signs of improvement with antibiotics only or using drainage procedures either through DJ stenting or pigtail catheter placement within 1 week were included in the responder's group. Pigtail catheterization was also grouped as "early" and "late," depending upon the time of insertion. Pigtail catheterization within 24 h of patient admission was considered early, and any time after 24 h of admission was considered late. The nonresponder's group consisted of the patients who died or had progressive worsening of symptoms 48 h after pigtail catheter placement or required nephrectomy. The differences in the baseline characteristics, clinical features, biochemical and radiological data, management modalities, and outcomes were compared between the two groups. Statistical analysis was done using a sample *t*-test and chi-square test, and *P* value <0.05 was considered statistically significant.

RESULTS

A total of 51 patients of EPN were studied and were divided into responders and nonresponders groups based on their

Table 1: Demographic profile, clinical features, and biochemical parameters of the patients

	Total (51 patients)	Responders (40 patients)	Nonresponders (11 patients)	*P* value
Age	53.96 ± 10.24	52.25 ± 10.78	60.18 ± 4.11	0.02
Sex (male/female)	18/33	16/24	2/9	
Fever	48	37	11	0.871
Flank pain	43	35	08	0.721
Altered consciousness	15	07	08	0.016
Shock	13	4	9	0.0009
Flank tenderness	42	33	9	0.986
Diabetes mellitus	45	36	9	0.850
Hypertension	21	16	5	0.835
Hemoglobin (g/dL); mean ± SD	9.83 ± 2.29	10.23 ± 2.21	8.4 ± 2.04	0.017
Total leukocyte count (per cubic millimeter); mean ± SD	16,119 ± 4892	19,272 ± 5417	17,252 ± 4425	0.262
Sr. creatinine (mg/dL); mean ± SD	2.99 ± 1.94	2.76 ± 1.63	4.43 ± 3.04	0.017
Thrombocytopenia	17 (33.3%)	8 (20%)	9 (81.8%)	0.013
Fasting blood sugar (mg/L); mean ± SD	225.3 ± 73.9	213.17 ± 71.4	239.81 ± 68.18	0.274

SD: standard deviation

clinical progression and outcome. Out of 51 patients, 40 patients were in the responders group, and 11 patients were in the nonresponders group. The demographic profile and the clinical spectrum of the included patients are shown in Table 1. The mean age of EPN patients was 53.96 ± 10.24 years, and out of 51 patients, 33 patients were females (64.7%). Fever (94.1%) was the most common presenting symptom, followed by flank pain (84.3%), and diabetes was the most common associated comorbidity (84.3%), followed by hypertension (41.1%). Among the responder's and the nonresponder's group, a significant difference was seen in terms of age, presentation of altered consciousness and shock, average hemoglobin, average serum creatinine, and presence of thrombocytopenia. The mean age in nonresponder's group was higher, 60.18 ± 4.11 years, as compared to 52.25 ± 10.78 years in the responder's group (*P* value = 0.02). Altered consciousness was seen in eight patients in the nonresponder's group as compared to seven patients in the responder's group (*P* value = 0.016). Nine patients in the non-responder's group, as compared to four patients in the responder's group, were in shock at the time of presentation (*P* value = 0.0009). The average hemoglobin in the non-responder's group was lower, 8.4 ± 2.04 mg/dL, as compared to the average hemoglobin in the responder's group, 10.23 ± 2.21 mg/dL (*P* value = 0.017). The average serum creatinine in the non-responder's group was 4.43 ± 3.04 mg/dL, higher as compared to the average serum creatinine in the responder's group, 2.76 ± 1.63 mg/dL (*P* value = 0.017). Thrombocytopenia was seen in nine patients in the nonresponders group as compared to eight patients in the responder's group (*P* value = 0.013). In our study, the most commonly encountered organism on urine culture was *E. coli*, found in 33 (64.7%) patients, followed by *Proteus mirabilis*, found in eight (15.6%) patients. Other organisms included *Klebsiella pneumoniae*, *Pseudomonas*, anaerobic and mixed bacterial agents.

Table 2: Radiological classification of patients according to the classification by Huang and Tseng

	Total (51 patients)	Responders (40 patients)	Nonresponders (11 patients)	*P* value
Class 1	17	17	0	0.03
Class 2	12	12	0	0.076
Class 3A	10	6	4	0.1
Class 3B	11	5	6	0.02
Class 4	1	0	1	0.06
Nephrolithiasis	18	14	4	0.953

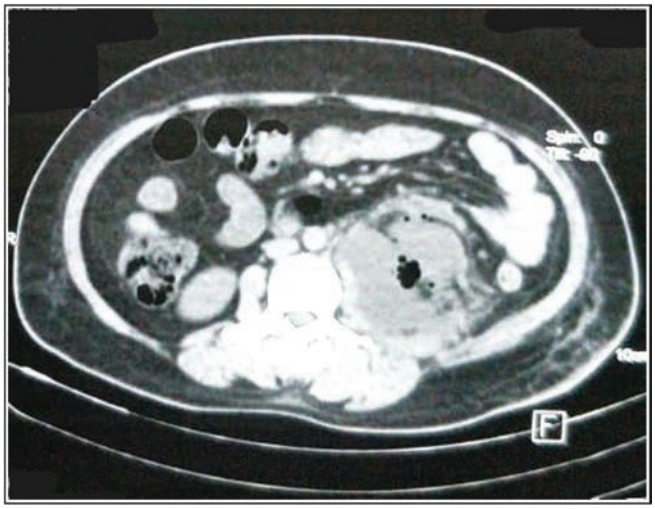

Figure 1: CT scan showing class 1 EPN with gas confined to the pelvicalyceal system of the left kidney

Table 2 shows the categorization of patients into four groups as per Huang and Tseng classification.[9] Out of total 51 patients, 17 (33.3%) patients were categorized as class 1 [Figure 1], and 12 (23.5%) patients were categorized as class 2 [Figure 2]. In class 3A, there were 10 (19.6%) patients [Figure 3]; in class 3B, there were 11 (21.5%) patients, and one (1.9%) patient was in class 4 category. In the responder's group, 29 (72.5%) patients were in class 1 and class 2 categories, while all of the patients in the nonresponder's group were either in class 3 or class 4.

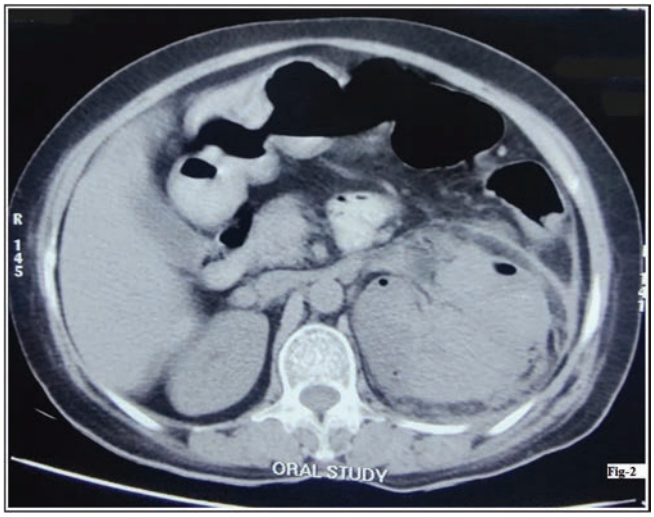

Figure 2: Class 2 EPN on CT scan showing gas in the left renal parenchyma

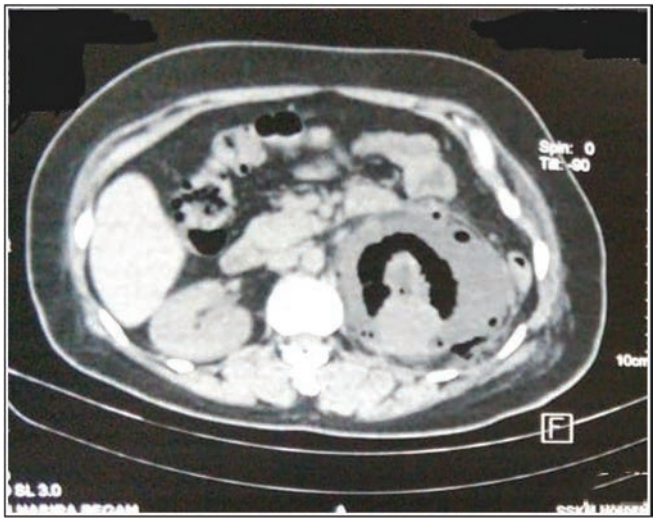

Figure 3: Class 3A EPN on CT scan showing the collection of gas outside the renal capsule of left kidney

Patients were managed in a stepwise manner according to the severity of infection and associated comorbidities [Tables 3 and 4]. In our study, 13 (25.4%), patients showed a response with antibiotics only. DJ stenting was done in 5 (9.8%) patients, and pigtail catheterization was done in total 33 (64.7%) patients, with early catheterization in 23 patients and late catheterization in 10 patients. Out of 23 patients with early pigtail catheterization, 18 patients responded to the treatment, while five were nonresponders (*P* value = 0.02). However, in patients with late pigtail catheterization, there was no significant difference seen in the response; out of total 10 patients, five responded and five did not respond to the treatment (*P* value = 1). Out of total 51 patients, nephrectomy was needed in eight (15.68%) patients. The initial treatment for each of these patients was pigtail catheterization, but when failed to respond, nephrectomy was performed. The mortality rate in our study was 9.8%, with the death of five patients.

Table 3: Management and outcome of patients of EPN

	Total (51 patients)	Responders (40 patients)	Nonresponders (11 patients)	*P* value
Antibiotics only	13	13	0	0.065
DJ stenting	5	4	1	0.934
Pigtail catheter	33	23	10	0.366
Nephrectomy	8	0	8	0.00001
Mortality	5	0	5	0.0002

EPN: emphysematous pyelonephritis, DJ stent: double J stent

Table 4: Outcome of early versus late pigtail drainage in EPN patients

	Total (33 patients)	Responders (23 patients)	Nonresponders (10 patients)	*P* value
Early pigtail catheter	23	18	5	0.02
Late pigtail catheter	10	5	5	1.00

EPN: emphysematous pyelonephritis

DISCUSSION

EPN is a necrotizing renal infection most commonly caused by *E. coli* and characterized by the presence of gas in the renal system.[10,11] There is the preponderance of EPN known in females, presumably due to their increased susceptibility to urinary tract infection. As reported in other studies, the majority of the patients (64.7%) in our study were females, and diabetes was the most commonly associated comorbidity.[4,5,7,9]

In our study, we found a statistical difference in the mean age and average hemoglobin levels among the responders and nonresponders groups. The other factors associated with poor prognosis were thrombocytopenia, raised serum creatinine levels, shock, and altered sensorium at the time of presentation. The findings are similar to the study done by Huang and Tseng, where the initial presentation of thrombocytopenia, disturbance of consciousness, and shock were associated with significant mortality.[9]A study by Sokhal *et al.*[12–14] and various other studies in the past have also reported the above parameters to be associated with poor prognosis. Our study adds up to the available evidence and points that the above factors should be kept in mind while choosing the appropriate management strategy.

In 2000, Huang and Tseng[9] reported a tendency to higher mortality and failure rates of percutaneous drainage (PCD) as we move from class 1 to class 4 disease. We followed the classification of Huang and Tseng and found the results to be similar. Patients with class 1 EPN had the best prognosis, and the highest mortality was seen in class 4 EPN.

There is no current consensus on the ideal management of EPN. Earlier studies focused on aggressive surgical intervention with medical management of EPN for a good outcome. In 1986, a study by Klein *et al*.[15] reported a mortality rate of 71% in medically treated patients compared to 29% in those surgically treated. In recent years more importance is being given to minimally invasive nephron-preserving approaches like PCD. Fluoroscopically guided PCD for treating EPN was first described by Hudson *et al*.[16-18] and later many series showed good outcomes with US or CT-guided PCD. Following the widespread adoption of PCD in the management of EPN, there has also been a decline in the associated mortality rate.[19]

In this study, we treated the patients in a step-wise manner, starting from conservative management and reserved nephrectomy for patients who did not respond to the above treatment. We were able to effectively manage a large number of patients with broad-spectrum antibiotics with or without early pigtail drainage. We found a statistically significant difference in the outcome of the patients with early pigtail drainage. Early pigtail drainage led to better results and a lower mortality rate. In this study, nephrectomy was required in eight patients, and the mortality rate was 9.8%, which is significantly less than what has been reported in the literature before. The lower mortality rate in our study could be attributed to the better accessibility to the health care system nowadays, easy availability of imaging modalities like CT scan leading to early diagnosis, early start of potent broad-spectrum antibiotics, and early pigtail drainage. However, the study also had some limitations, including a small patient population and a lack of long-term follow-up. Also, due to the ambispective nature of this study, some of the data was also gathered through retrospective analysis.

To conclude, the management of EPN should be tailored to each patient depending upon the presence of risk factors and radiological grading. Advanced age, lower hemoglobin levels, thrombocytopenia, raised serum creatinine levels, altered mental status, and presence of shock at the time of presentation can be used as a score for poor prognosis. A large number of patients can be effectively managed with the early use of broad-spectrum antibiotics and early pigtail drainage. Nephrectomy should be reserved for patients who do not respond to conservative management or who have advanced disease, class 3 or class 4 on CT scan, and multiple risk factors.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Thyroid-like follicular carcinoma of kidney

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Abstract

Renal cancer resembling thyroid-like tumor of the kidney is extremely rare. This type of renal tumor shows the morphologic features that resemble follicular carcinoma of thyroid. In our case, a 62-year-male patient presented with flank pain with all blood parameters in normal range. Chest X-ray were normal, contrast enhanced computed tomography report showed well defined hyperdense lesion of size 26 mm × 21 mm showing homogenous enhancement (hu 46–126 from pre to post contrast) noted in lower pole of right kidney. Patient underwent radical nephrectomy, histopathological examination suggestive of thyroid-like follicular carcinoma with IHC markers as TTF1-negative, CK7-negative, and PAX8-negative. Patient was referred to Department of Radiotherapy for further management. Immunohistochemical staining studies in the literatures showed that this tumor consistently expressed the transcription factor PAX-8 but did not express the thyroid-specific antibodies TG and TTF-1. Most tumors with diameters of more than 4 cm or associated with invasive growth or distant metastasis are treated mainly with radical nephrectomy, combined with the corresponding regional lymph node dissection. Surgical treatment is still the preferred therapeutic method. The disease seems to have a good prognosis.

Keywords: Carcinoma, follicular, kidney

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INTRODUCTION

Renal cell carcinoma accounts for 3%–4% of all neoplasms.[1]

Renal cancer resembling thyroid-like tumor of the kidney is extremely rare; however, there are only few case reports regarding this type of tumor as it is a rare entity. It has been listed as pp9-88 in current World Health Organization classification of kidney tumors. This type of renal tumor shows the morphologic features that resemble follicular carcinoma of thyroid.[2]

CASE REPORT

A 62-year-old female patient reported to outpatient department with chief complaint of pain in right flank since 3 months. On physical examination, her abdomen was smooth without any tenderness or flank masses. All blood tests were within normal limits, hemoglobin: 11.1 g/dL, creatinine: 0.61 mg/dL, and liver function test are normal, no history of weight loss, no history of hematuria, no respiratory difficulty and the rest of the examination was unremarkable.

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On radiological examinations: chest X-ray P/A view done which is normal. Ultrasound whole abdomen showed multiple large cyst with echogenic mural noted in left kidney s/o complex cyst.

Contrast enhanced computed tomography (CECT) report showed well defined hyperdense lesion of size 26 nm × 21 mm showing homogenous enhancement (hu 46–126 from pre to postcontrast) in venous phase noted in lower pole of right kidney [Figure 1].

The patient underwent radical nephrectomy, histopathological examination suggestive of thyroid-like follicular carcinoma with IHC markers as TTF1-negative, CK7-negative, and PAX8-negative [Figure 2A and B].

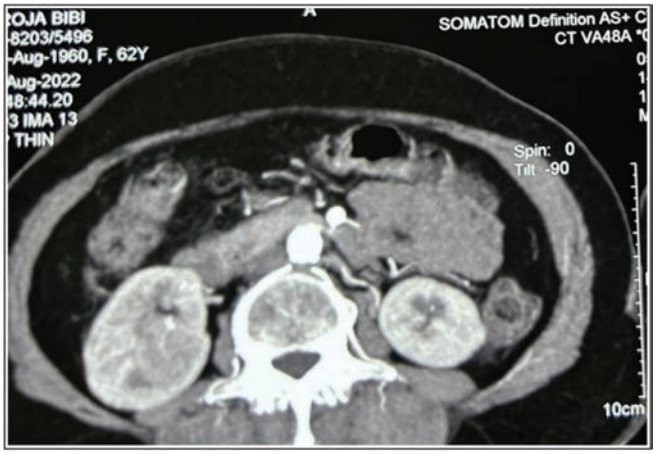

Figure 1: Well defined hyperdense lesion of size 26 mm × 21 mm showing homogenous enhancement (hu 46–126 from pre to post contrast) in venous phase noted in lower pole of right kidney

The patient was referred to Department of Radiotherapy for further management of the case, where patient was asked to follow up every 3 months with CECT of whole abdomen, chest X-ray and basic blood investigations.

DISCUSSION

Renal cancer resembling follicular carcinoma of thyroid occurs most commonly in females, the average of such type of cancer is found within the 4th decade (19–83 years of age) with female gender most commonly affected.[2] This is in contrast with renal cell carcinoma which is more common in male patients. The common symptoms are abdominal pain and hematuria.[3] The patient was only having abdominal pain in this case. The tumor size was 26 mm × 21 mm. Thyroid-like renal cell carcinoma has no specific differentiating feature on radiodiagnosis. Hence histopathological examination becomes mandatory.[4]

Microscopic morphology revealed thyroid follicle-like structures of varying sizes, containing an eosinophilic, amorphous, colloid-like substance. The morphology was similar to that of well-differentiated thyroid follicle cancer.[5,6] Immunohistochemical staining studies in the literature showed that this tumor consistently expressed the transcription factor PAX-8 but did not express the thyroid-specific antibodies TG and TTF-1.[4] However in our case, this patient is PAX-8 negative.

Regarding treatment and prognosis, surgical resection is the main treatment method for this type of tumor. Most tumors with diameters of more than 4 cm or associated with invasive growth or distant metastasis are treated mainly with radical nephrectomy, combined with the corresponding regional

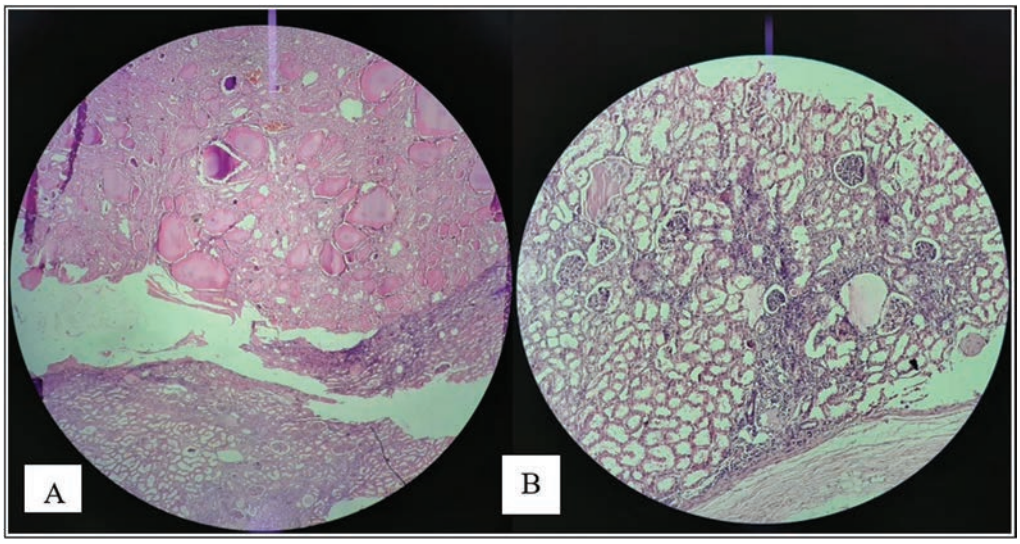

Figure 2: (A) Tumor is composed of micro and macro follicles of varying sizes with colloid-like material (hematoxylin-eosin, original magnification ×10), (B) hematoxylin-eosin, original magnification ×20

lymph node dissection.[6] This tumor has a very low rate of recurrence and distant metastases, still a regular follow-up is needed to rule out any recurrence or distant metastases.[7]

CONCLUSION

Thyroid-like carcinoma of the kidney, which is a rare variant of renal cell carcinoma, has unique morphological and immunohistochemical characteristics. Radiological imaging often does not provide enough information to differentiate the lesion as benign or malignant. Confirmation depends on pathological examination with immunohistochemistry. Surgical treatment is still the preferred therapeutic method. The disease seems to have a good prognosis; however, the number of cases is small and the follow-up time is still short.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

Co-existing nephrolithiasis and mucinous adenocarcinoma of kidney: A case report

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Abstract

Primary mucinous adenocarcinoma of the renal pelvis is a rare malignant disease and it is difficult to diagnose preoperatively. There are still no characteristic symptoms, radiological features, or standard treatment. The prognosis of mucinous adenocarcinoma is poor. We reported a case of a 62-year-old male patient with a long-standing history of kidney calculi with mucinous adenocarcinoma of kidney. The current literature is reviewed.

Keywords: Malignancy of kidney, mucinous adenocarcinoma, nephrolithiasis

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INTRODUCTION

Malignant tumor arising from the renal pelvis includes transitional cell carcinoma (85%–90%), squamous cell carcinoma (10%–15%), and adenocarcinoma (<1%). Adenocarcinoma of the kidney can be sub-classified as tubulovillous, mucinous, and papillary non-intestinal. To date, only ~100 cases of mucinous adenocarcinoma have been reported.[1]

Etiopathogenesis of mucinous adenocarcinoma is unclear, yet it is thought to originate from intestinal metaplasia in the transitional epithelium.[2] It is difficult to diagnose preoperatively because there are neither specific symptoms nor laboratory and radiological findings.

Herein, we present a case of mucinous adenocarcinoma arising from the renal pelvis and associated with renal calculus.

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CASE PRESENTATION

A 62-year-old male patient came with complaints of on and off bilateral flank pain for the last 15 years. The intensity of pain was gradually increased in the last 6 months. Physical examination revealed no positive findings. The patient was evaluated for the above complaints and found to be bilateral nephrolithiasis and bilateral hydronephrosis with deranged kidney function. Bilateral double J stenting has been done preoperatively. Ultrasonography report was suggestive of bilateral hydronephrosis with 11 mm calculus in the right renal pelvis and 16 mm calculus in the left renal pelvis [Figure 1]. Impression of non-contrast computed tomography report is 15 mm × 12 mm calculus in the right renal pelvis and large stag horn calculus of size 33 mm × 32 mm (Hounsfield unit+1440) in the left renal pelvis and thinning of cortex with bilateral hydronephrosis [Figure 2]. Right percutaneous nephrolithotomy (PCNL)

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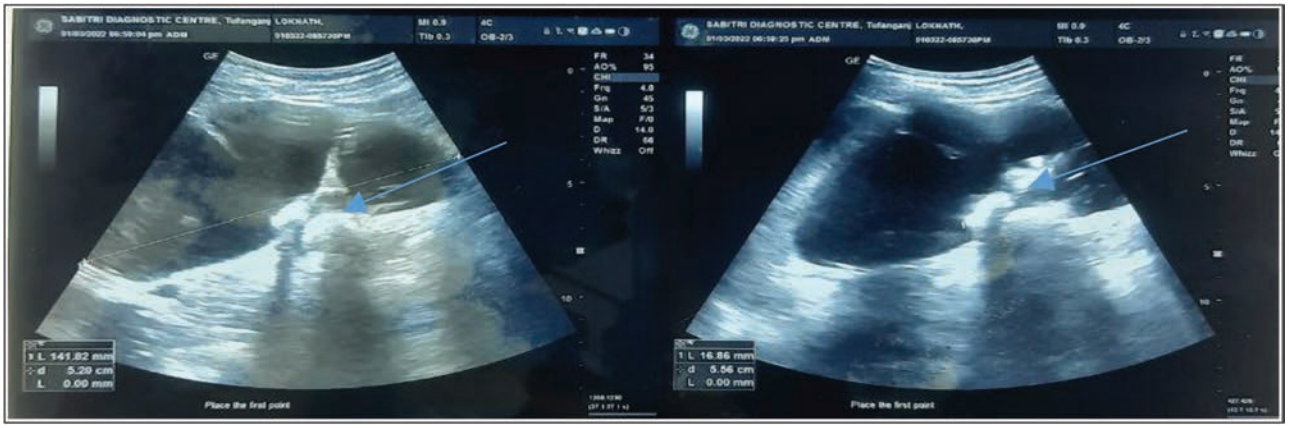

Figure 1: Bilateral hydronephrosis with 11 mm calculus in the right renal pelvis and 16 mm calculus in the left renal pelvis, marked by arrow

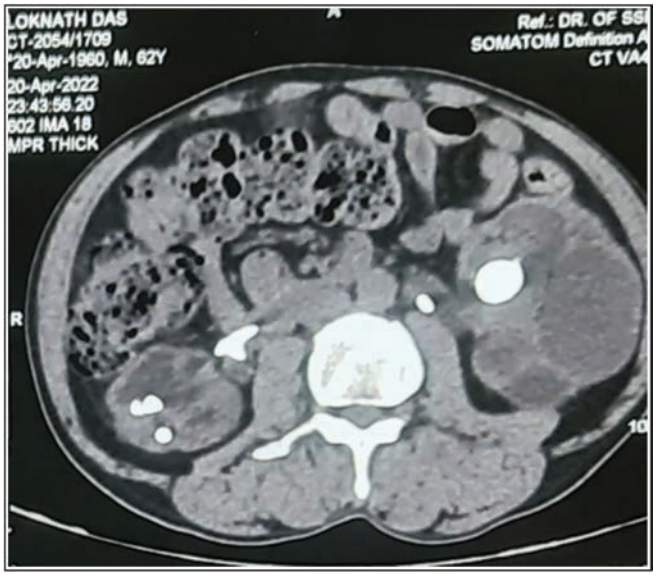

Figure 2: Non-contrast computed tomography report is 15 mm × 12 mm calculus in the right renal pelvis and large stag horn calculus of size 33 mm × 32 mm (Hounsfield unit+1440) in the left renal pelvis and thinning of cortex with bilateral hydronephrosis

was done. The intraoperative and postoperative course was uneventful. After 15 days of the right PCNL, the left PCNL was done. Around 500 ml of gelatinous material aspirated from amplatz sheath during surgery. Procedure abundant due to suspiciousness of malignancy based on intraoperative findings. magnetic resonant imaging kidney, ureter, bladder report suggestive of a moderately dilated right renal pelvis and large fluid debris filling the left kidney (MRI was done after right PCNL). No evidence of mass in bilateral kidneys [Figure 3]. The gelatinous aspirate was sent to the laboratory for the estimation of drain fluid carcino embryonic antigen level, which was significantly high (>1000 Ng/mL). Left nephrectomy was done because of suspiciousness of malignancy. Histopathological report of the gross specimen confirms the diagnosis of mucinous adenocarcinoma [Figure 4]. The patient was discharged from the hospital in stable condition.

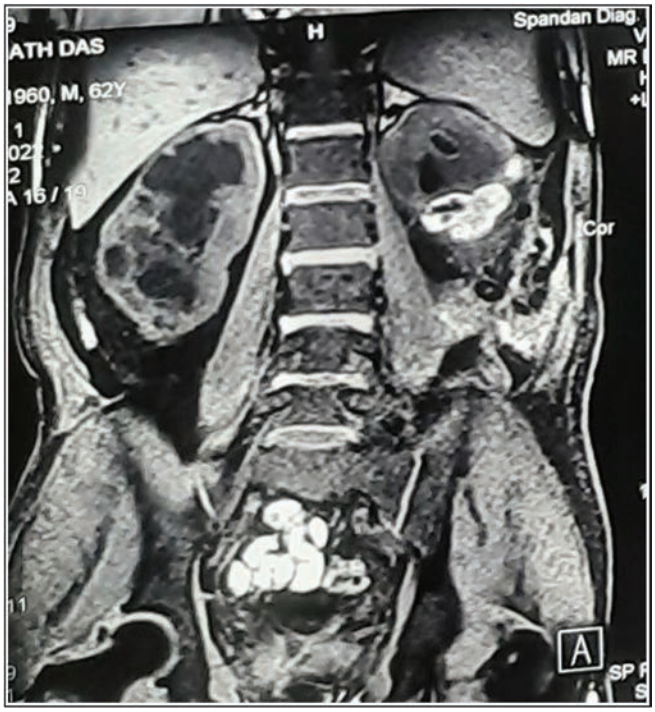

Figure 3: MRI image showing left side kidney stone and no evidence of mass in bilateral kidneys

DISCUSSION

Primary mucinous adenocarcinoma of the renal pelvis is a rare disease with fewer than 100 cases reported to date. Mucinous adenocarcinoma, generally seen in the colorectal and ovarian regions, is characterized by abundant mucous secretion comprising more than 50% of the tumor volume.[3,4]

Renal mucinous adenocarcinoma is related to chronic irritation by nephrolithiasis, infection, hydronephrosis, and inflammation. It is derived from meta-plastic endothelium.[5]

There are no characteristic radiological features of primary mucinous adenocarcinoma.[6]

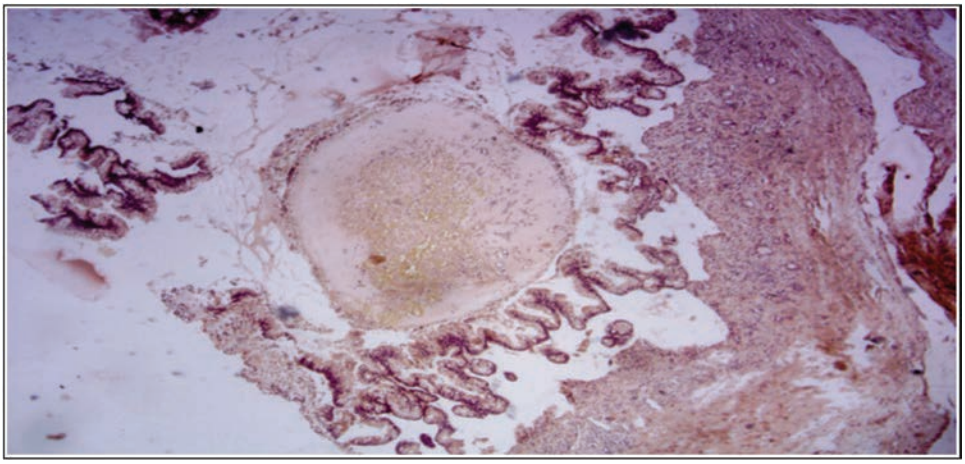

Figure 4: Image showing glands, papillary structure lined by atypical cells having nuclear pleomorphic, vesicular nuclei, and intracytoplasmic mucin. The gland and papillary structures infiltrate the renal parenchyma. Extracellular mucin also seen (<50%), magnification 10×

Our patient presented with multiple renal pelvic calculi and severe hydronephrosis with cortical thinning. According to most of the reported cases, hydronephrosis and non-functional kidney caused by renal calculi were diagnosed by computed tomography. Only after pathologic analysis, could primary mucinous adenocarcinomas of the renal pelvis be diagnosed.[7] Primary kidney mucinous adenocarcinoma may express carcino embryonic antigen, but the relationship between two has not been established yet.[8] Akan *et al*.[9] suggested that, as such there are no definite diagnostic radiological criteria to diagnose mucinous cystadenocarcinoma of kidney, and there is no definitive treatment, so it should be individualized. Partial nephrectomy or cyst excision can be performed if malignancy is suspected. Fine-needle aspiration biopsy should be performed first if the cyst compresses the collecting system. If needle aspiration fails due to viscous cyst content or if the malignant material is extracted, surgical specimens can be obtained through the operation. In our case clear evidence has been shown that the tumor can cause the elevation of carcino embryonic antigen level. These findings can be used as simple method to monitor disease progression. Mucinous adenocarcinoma is an aggressive tumor and has a poor prognosis compared with other carcinoma of kidney. Early diagnosis and radical nephrectomy are the key procedures of management. The prognostic factors include tumor stage, size of tumor, and grade. If we can approach these as early as possible, the tumor can be resected with negative margins.

CONCLUSION

Mucinous adenocarcinoma of the renal pelvis is rare malignancy. The pathogenesis is considered to be associated with long-standing infection, inflammation, and stone disease. Preoperative diagnosis is difficult; thus, physicians should still keep in mind this possibility when the patient has prolonged stone compaction. Adjuvant therapy has not been established; therefore, an early operation is the main effective treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Solitary fibrous tumor of kidney

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Abstract Solitary fibrous tumor is a rare mesenchymal tumor usually described in the thoracic cavity. They may present in the genitourinary system with hematuria, enlarging abdominal mass and flank pain. Here, we report a case of 36-year-male patient with an incidental diagnosis of a left renal mass with histopathology and immunohistochemistry suggestive of a solitary fibrous tumor in a radical nephrectomy specimen.

Keywords: Benign spindle cell, renal cell cancer, solitary fibrosis tumor

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INTRODUCTION

Most of the fibrous tumors originate from the pleura, but tumors originating from genitourinary systems such as the kidney, urinary bladder, and prostate have also been reported.[1] Clinically, they are diagnosed as renal cell carcinoma. Renal solitary fibrous tumor (SFT) are extremely rare. To date, only 106 cases of renal SFT have been reported.[2] Definitive diagnosis can be made by pathological examinations including immunohistochemical and molecular techniques.

CASE REPORT

A 36-year-old male patient presented to the outpatient department of general surgery with chief complaints of dyspepsia and pain in epigastrium for 6 months. On evaluation was found to have a left renal mass and was referred to urology department for the management of the same. On examination abdomen was soft and nontender and no mass was palpable. There was no history of dyspnea on exertion.

Ultrasound abdomen showed a large hypoechoic nodular mass involving the superior and mid pole of left kidney about 6.5 cm × 5.9 cm × 6.0cm, compressing the superior and mid pole calyx. Mass was predominantly solid in nature. Contrast enhanced computed tomography (CECT) of abdomen and pelvis scan showed a large heterogeneously enhancing predominantly solid mass of size 6 cm × 6.5 cm × 6.3 cm arising from the mid pole of left kidney with an exophytic component with extension into upper and lower pole calyces. Renal vein and inferior vena cava were normal in caliber. No significant lymphadenopathy noted [Figure 1].

Magnetic resonance imaging (MRI) of abdomen and pelvis was suggestive of well-defined heterogenous mass lesion in the interpolar region of the left kidney of size (6.5 cm × 6.8 cm × 7.1cm) with intact perinephric fascia with no extension to renal vein or inferior vena cava. No pulmonary

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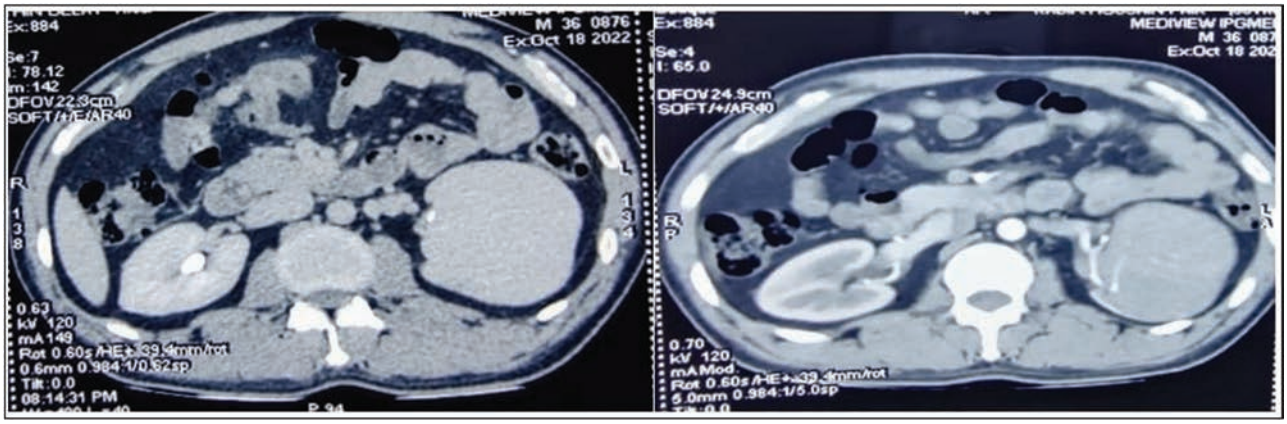

Figure 1: CECT of abdomen—large heterogeneously enhancing predominantly solid mass of size 6 cm × 6.5 cm × 6.3 cm arising from the mid pole of left kidney with exophytic component with extension into upper and lower pole calyces

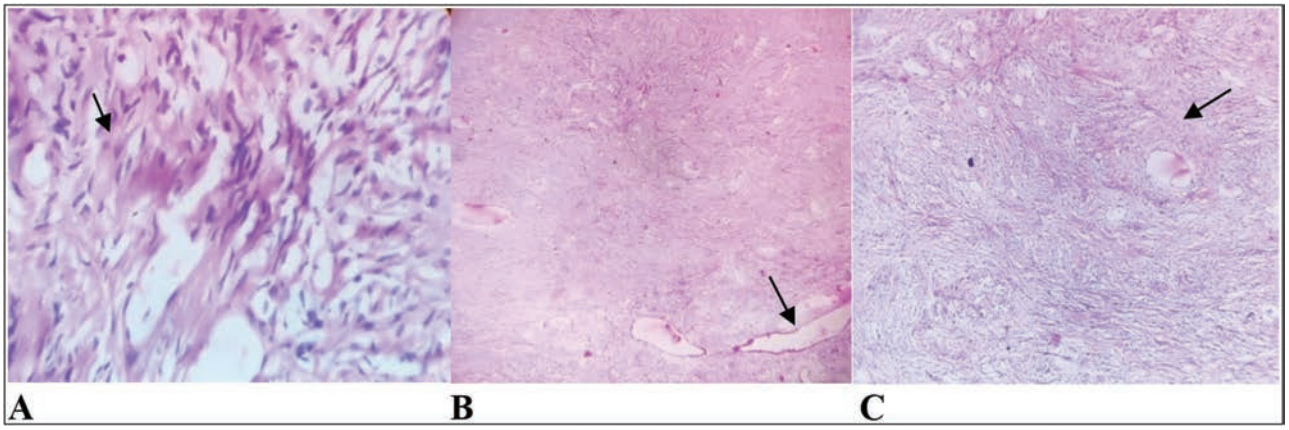

Figure 2: Hematoxylin and eosin stain showing. (A) (HE ×40) Circumscribed spindle cell neoplasm composed of bland fusiform spindle cells arranged in short fascicles and haphazard pattern (arrow mark). (B) (HE ×10) Staghorn-like blood vessels are identified within the tumor (arrow mark). (C) (HE ×10) Collagen bundles are seen traversing in between tumor cells (arrow mark)

metastasis seen on high resolution CT thorax. All blood investigations were within normal limits.

The patient underwent left radical nephrectomy. Intra operatively large solid mass was noted arising from upper and mid pole of left kidney. Intra operative and postoperative course was uneventful and the patient was discharged on postoperative day 4.

Histopathological examination of the specimen showed features of a circumscribed spindle cell neoplasm composed of bland fusiform spindle cells arranged in short fascicles and haphazard pattern. Few collagen bundles were seen traversing in between tumor cells, few dilated staghorn like blood vessels were identified within the tumor. No evidence of increased mitotic activity, atypia, or necrosis is identified. Sections from ureter cut margins, renal pelvis, hilum, perinephric fat, and fascia of gerota were unremarkable [Figure 2]. These features were suggestive of benign spindle cell neoplasm favoring solitary fibrous tumor of left kidney. Immunohistochemistry (IHC) markers CD34 and Vimentin was positive whereas Desmin and S-100 were negative.

The patient is on regular follow-up for the past 6 months with no evidence of local recurrence or distant metastasis.

DISCUSSION

Solitary fibrous tumor was first reported in 1931 from pleura and in 1996 first SFT was reported from kidney.[3] It was found that all SFTs whether pleural or extrapleural have same immunohistochemical, morphologic features, and biologic behavior.[4] 10%–15% of all SFTs are malignant. The criteria for malignancy include increased cellularity, increased mitotic activity (more than 4 mitoses on 10 high power fields), pleomorphism, hemorrhage, and necrosis.[5]

Small renal SFTs are usually asymptomatic and some present with palpable mass, flank pain and often hematuria that is why the diagnosis is delayed in the majority of cases.[6] Diagnosis of SFT on the basis of ultrasonography, CT

scan, and MRI scan is not specific but helpful only in the evaluation of tumor extension. Solitary fibrous tumor on unenhanced CT scan shows soft tissue attenuation and may show strong enhancement on enhanced CT with associated cysts, necrosis or hemorrhage.[7]

Almost all renal SFT cases being usually misdiagnosed as renal cell carcinoma as their diagnosis is not specific on radiological investigations and majority are treated with radical or partial nephrectomy depending on the size and location of the tumor.[6] Surgical resection is the standard treatment of renal SFTs, and complete resection can be associated with an excellent prognosis, even if the renal SFT is histologically turned out to have malignant potential.[6]

Histologically, SFTs were distinguished by hyper cellular stroma of spindles cells with no pattern architecture.[8] Typical immunohistochemical characteristic is high positivity for CD-34 IHC marker, regarded as core to the diagnosis of SFT.[8] In this case IHC markers CD34 and Vimentin were positive whereas Desmin and S-100 were negative.

Malignancy has been reported in some renal SFT so careful follow-up is a must to evaluate for local recurrences and distant metastasis.

CONCLUSION

Solitary fibrous tumor of kidney is a rare mesenchymal tumor with good prognosis. Definitive diagnosis can be made only with pathological studies. Complete surgical resection is the treatment for renal SFTs. There is a remote possibility of malignant transformation and local recurrence so follow up of patients with renal SFT is important.

Financial support and sponsorship
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Conflicts of interest
There are no conflicts of interest.

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Case Report

Tamsulosin: An unthinkable cause of priapism

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Abstract

Priapism is the full or partial erection that continues for more than 4 h beyond sexual stimulation and orgasm or is unrelated to sexual stimulations. Most commonly, it is idiopathic in nature. Few drugs are also associated with priapism. Here, we are presenting a case report of tamsulosin-associated priapism in 36-year-old men.

Keywords: Ischemic priapism, phenylephrine, priapism, tamsulosin

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INTRODUCTION

Priapism is full or partial erection that continues more than 4 h beyond sexual stimulation and orgasm or is unrelated to sexual stimulations.[1] The incidence of priapism in the general population is 0.5–0.9 cases/100,000 person-years.[1] Priapism is of three types: ischemic, nonischemic, and stuttering. The most common cause of priapism is idiopathic. It accounts for more than 50% of cases. Drugs-induced priapism is the second-most common, accounting for >30% of cases.[2] Tamsulosin is the most commonly used drug in urological practice. It is considered one of the safest drugs, yet it is not free from side effects. It is associated with retrograde ejaculation, dizziness and postural hypotension, and very rarely priapism. The incidence of priapism seen with tamsulosin is <1 in 50,000[3] and 1 in 10,000.[4] Although rare, priapism, once developed, should be promptly evaluated and treated to prevent the development of penile fibrosis and erectile dysfunction.[5] The objective of this case report is to present a case of tamsulosin-induced ischemic priapism and add to the knowledge of medical science.

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CASE REPORT

A 36-year-old nonsmoker, nonalcoholic man without any comorbidities presented to emergency with unresolving painful erection of the penis for about 6 h. The patient had a history of dysuria, urgency, and frequency for which he was prescribed ofloxacin along with tamsulosin by his local physician. He had no history of the neurological, psychiatric or hematological ailment. He took a single dose of tamsulosin at night before his presentation at the emergency on subsequent day. He noticed erection when he woke up at 8 AM even without any sexual stimulation. He tried to achieve detumescence by masturbation but without success. Embarrassed, he presented in emergency with the erect penis with increasing intensity of pain and penile edema. By the time he arrived, 6 h had already passed.

At admission, examination showed: Temperature of 37.2°C, pulse of 110/min, blood pressure of 136/80 mmHg. Systemic examination was normal. Genital examination revealed a painful rigid erection with chordee without glans tumescence [Figure 1a]. Arterial blood gas done revealed ischemic priapism.

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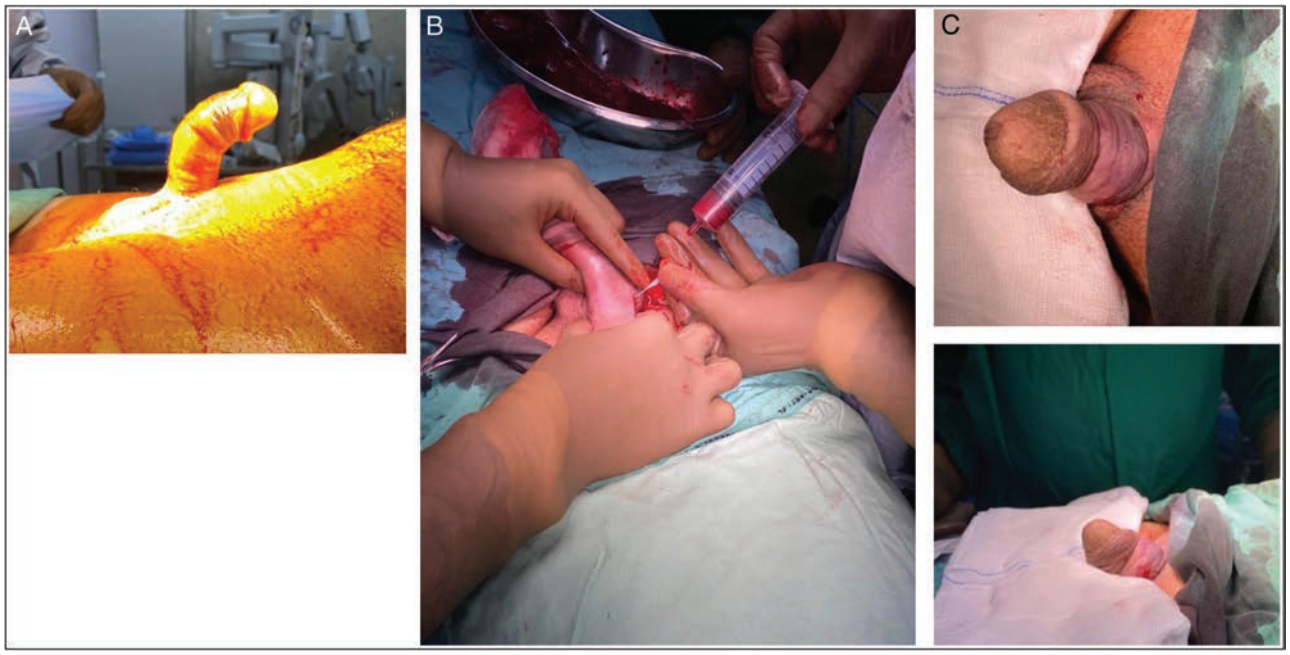

Figure 1: (a) Priapism (b) Priapism aspiration and irrigation (c) priapism resolution

Blood tests ruled out any blood dyscrasia. The patient was taken to operation theatre, initially aspiration and irrigation were attempted but failed [Figure 1b]. Hence, 1 ml phenylephrine (200 mcg/ml) injection was instilled intracavernously. Soon after instillation, detumescence was achieved, and the patient did not require any further procedures [Figure 1c]. The patient did not develop fresh priapism episodes while he was hospitalized. He was discharged with instructions not to indulge in sexual intercourse for the next few days and to avoid tamsulosin. In follow-up, the patient had no episodes of priapism and had normal erection with satisfactory sexual life.

DISCUSSION

Priapism is a prolonged painful erection lasting more than 4 h in the absence of sexual stimulation and remaining despite orgasm.[1] It is classified as ischemic, nonischemic, and stuttering priapism. The incidence of priapism in the general population is <1 case per 100,000 person-years.[1] Adverse effects of various medicines and recreational drugs are important causes of priapism. Common drugs causing priapism include intracavernosal injection of vasoactive substances such as phosphodiesterase inhibitors, antidepressants, cocaine, and alcohol and neurological and hematological conditions. Various alpha blockers also have also been implicated in causing priapism, commonly being prazosin, and terazosin.

In literature, we have found very few cases of priapism associated with tamsulosin also. Tamsulosin-associated priapism is dose and concentration independent, but the causal relationship between tamsulosin and priapism has been established.[6,7] In one of these cases, tamsulosin was associated with partial thrombosis of corpora cavernosa.[8] In our case patient did not have a history of comorbidities or use of the recreational drug. He had consumed tamsulosin 18–20 h before the presentation. Tamsulosin interferes with the detumescence mechanism mediated by adrenaline and noradrenaline by acting on corpora cavernosal alpha-adrenergic receptors. Looking at the previous case reports and our case report, it seems that the development of priapism is independent of tamsulosin doses. Hence even though priapism development related to tamsulosin is rare, the patient should be properly counseled of this rare possibility and advised to report immediately to emergency if it happens.

CONCLUSION

Even though tamsulosin is rarely associated with priapism, the patient should be counseled regarding that risk and they should remain vigilant.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Brief Report

Coexisting pseudoaneurysm and arteriovenous fistula following percutaneous nephrolithotomy

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Abstract

Percutaneous Nephrolithotomy (PCNL) is a common and safe treatment for large kidney stones .Though several complications are reported .Renal hemorrhage is the most common complication after PCNL with a incidence of 11.2% to 17.5%.There have been reports of post PCNL bleeding attributable to AV fistulas and pseudoaneurysms. Massive bleeding can occur in the early postoperative period (2 to 14 days after PCNL), and arteriovenous fistula formation as a late complication usually 6 weeks after PCNL . A 45 yrs old gentleman presented with bilateral flank pain ,right sided prone PCNL done . Then presented with post PCNL hematuria, angioemblosation done twice but again developed hematuria and diagnostic angiography done, and diagnosed as A-V fistula and coiling done. No post operative complications were seen. Angiography is the preferred method and has advantages as it can detect vascular lesions and immediately treated once they are detected .Early diagnosis and treatment of post PCNL hematuria is warrented to reduce morbidity and a successful outcome.

Keywords: Arteriovenous, DJ stenting, percutaneous nephrolithotomy

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is a common and safe treatment for large kidney stones.[1] Although several complications are reported, renal hemorrhage is the most common complication after PCNL with a incidence of 11.2%–17.5%.[2]

There have been reports of post-PCNL bleeding attributable to arteriovenous fistulas (AVFs) and pseudoaneurysms. Massive bleeding can occur in the early postoperative period (2–14 days after PCNL) and AVF formation as a late complication usually 6 weeks after PCNL.[3]

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CASE REPORT

A 45-year-old male presented with bilateral flank pain for the last 1 year. On evaluation, he was found to have bilateral multiple calculi and planned for bilateral PCNL (right followed by left PCNL). Right-sided prone PCNL with DJ stenting was done under GA. After discharge on POD 10, he developed hematuria and admitted. Computed tomography (CT) angiography was done [Figure 1]. On POD 20, angioembolization of posterior division of the right renal artery was done under LA. Hematuria subsided

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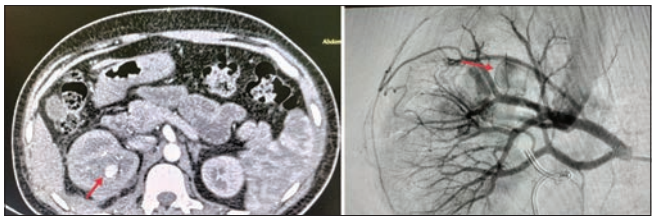

Figure 1: Arrow showing pseudoaneurysm

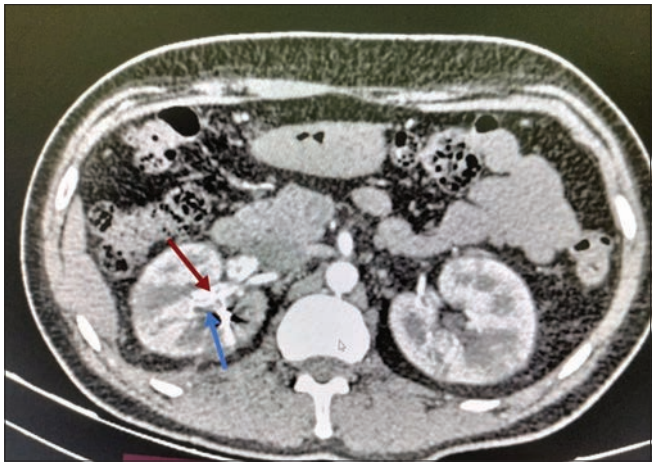

Figure 3: Red arrow – artery, and blue arrow – vein

after angioembolization, and he was discharged in stable condition.

After discharge, he again developed hematuria and fever and admitted after 3 weeks. Diagnostic angiography was done under LA and in the same setting re-embolization was done for the upper pole bleeding artery (leakage of dye through the previously coiled site) [Figure 2].

After discharge, he again developed gross hematuria from (November 11, 2022). He was admitted and evaluated and found to have newly developed AVF.

Figure 3 shows red arrow (artery) and blue arrow (vein). Figure 4 shows Diagnostic angiography; red arrow – artery, larger blue arrow – vein, smaller blue arrow – IVC (IVC: Inferior Vena Cava). Postcoiling, the patient was kept under close observation with weekly follow-up for 6 weeks without any complications.

DISCUSSION AND CONCLUSION

Vascular injuries such as PA and AVF are frequent complication after PCNL that need to be detected and managed. It is reported that diagnosis of vascular injuries is based on CT angiogram and then angiography. However, in this study, based on severity and continuity of bleeding, we use angiography without CT. Angiography

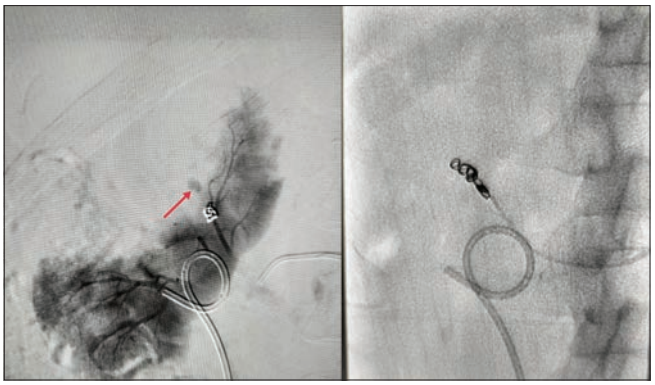

Figure 2: Pseudoaneurysm (left) and post-re-embolization (right)

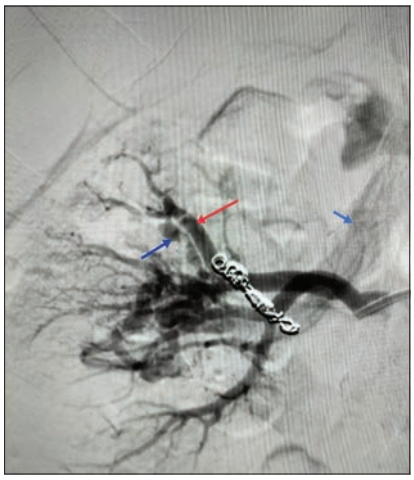

Figure 4: Diagnostic angiography; red arrow – artery, larger blue arrow – vein, smaller blue arrow – IVC (IVC: Inferior Vena Cava)

is the preferred method and has advantages as it can detect vascular lesions and immediately treated once they are detected. Early diagnosis and treatment of post-PCNL hematuria is warranted to reduce morbidity and a successful outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Clinical Image

Tubercular dactylitis with discharging sinuses: A very rare presentation of skeletal tuberculosis

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Abstract Skeletal tuberculosis is a common form after pulmonary and lymphnode involvement, but involvement of soft tissues is rarely seen after pediatric population. Tubercular dactylitis is such a lesion and needs consideration before ordering more costly investigations.

Keywords: Dactylitis, musculoskeletal involvement, tuberculosis

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A 20-year-old girl who had a history of low back pain, aggravating at night, fever with night sweats, diminished appetite, weight loss, pain and swelling of fingers and toes with serous discharge from multiple sinuses since last 6 months. She was treated with oral analgesic and antibiotics, without any improvement. On examination, she had poor nutritional status, moderate pallor, swelling of middle and ring fingers of left hand, ring finger of right hand, toes of right foot with discharging sinuses [Figures 1–3], and spinal deformity with gibbous formation at the lower lumber region [Figure 4], without lymphadenopathy or hepatosplenomegaly. Her laboratory reports showed hemoglobin 8 g/dl, total leukocyte 4400/mm, ESR 60 mm at 1st hour, positive Monteux test 22 mm (with 5TU); X-ray of chest was normal; lumbar spine showed disc space narrowing and anterior wedging at L2–L3 vertebrae—all suggestive of caries spine. Examination of both the hands and feet revealed spindle-shaped swelling of fingers suggestive of dactylitis and multiple discharging sinus [Figures 1–3]. Hence, she received a clinical diagnosis of spinal tuberculosis with tubercular dactylitis. Antitubercular therapy was started with spinal support and she was kept for a regular follow-up.

Skeletal tuberculosis is very much common in India, but the involvement of soft tissue of fingers and toes (dactylitis) is quite rare in adult population, although might be seen in the pediatric age groups.[1] Pain and swelling of the involved fingers and toes were reported as the most common presenting features, with sinus formation in some cases.[2] These lesions might cause lytic bony expansion, leading to a thinned-out cortex and bony destruction (spina ventosa) on X-ray.[3] Hence, dactylitis of possible tubercular etiology must be considered as one of the differential diagnoses, especially in our country where tuberculosis is an endemic

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Figure 1: Right hand showing dactylitis of ring finger and dicharging sinus.

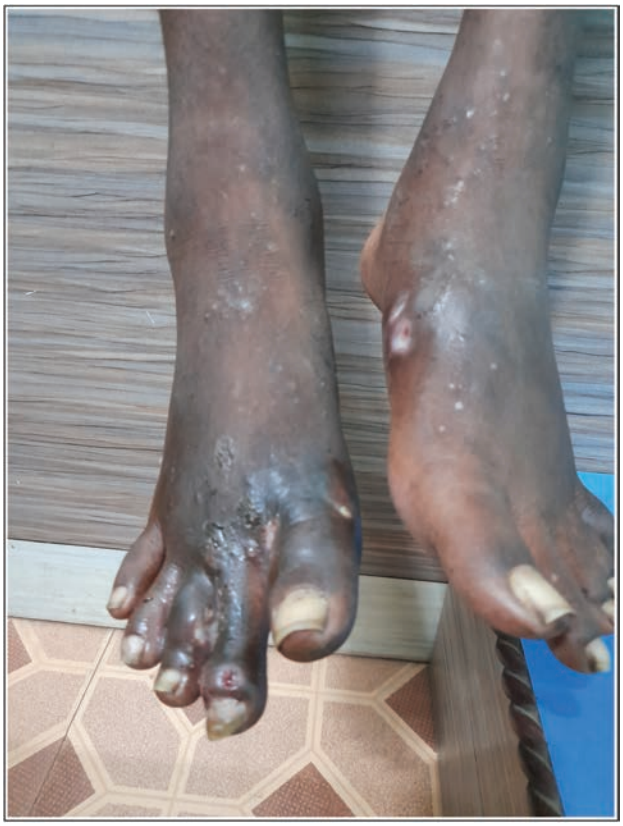

Figure 3: Feet showing dactylitis involving toes.

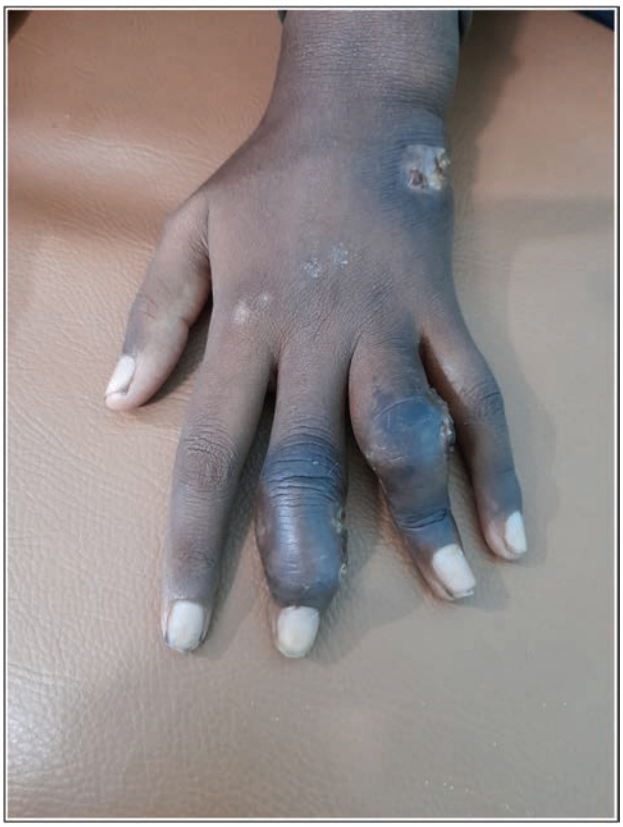

Figure 2: Left hand showing dactylitis involving ring and index finger and sinus.

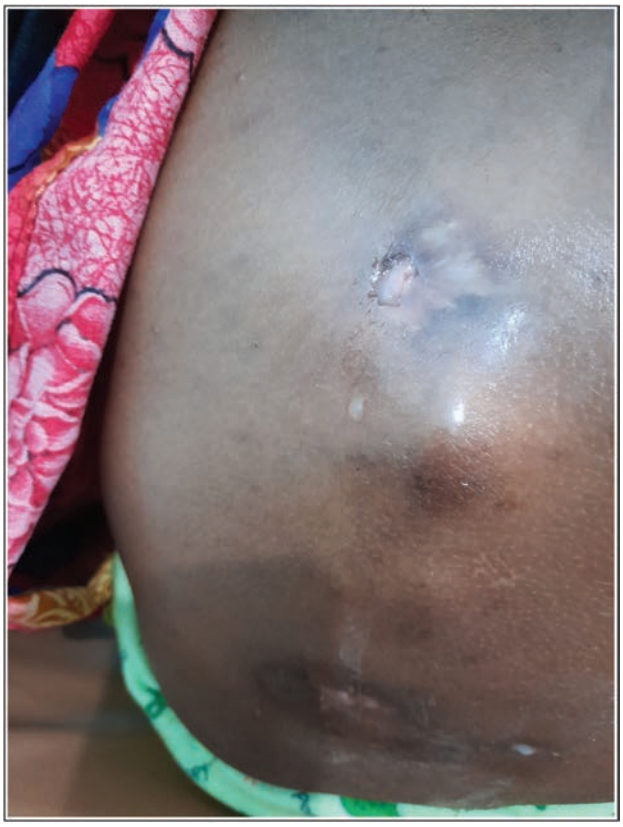

Figure 4: Spinal deformity and discharging sinus.

disease, before ordering more costly investigations; moreover, in such cases, early diagnosis is essential to prevent further bony destruction and progression of a treatable disease.[4]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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