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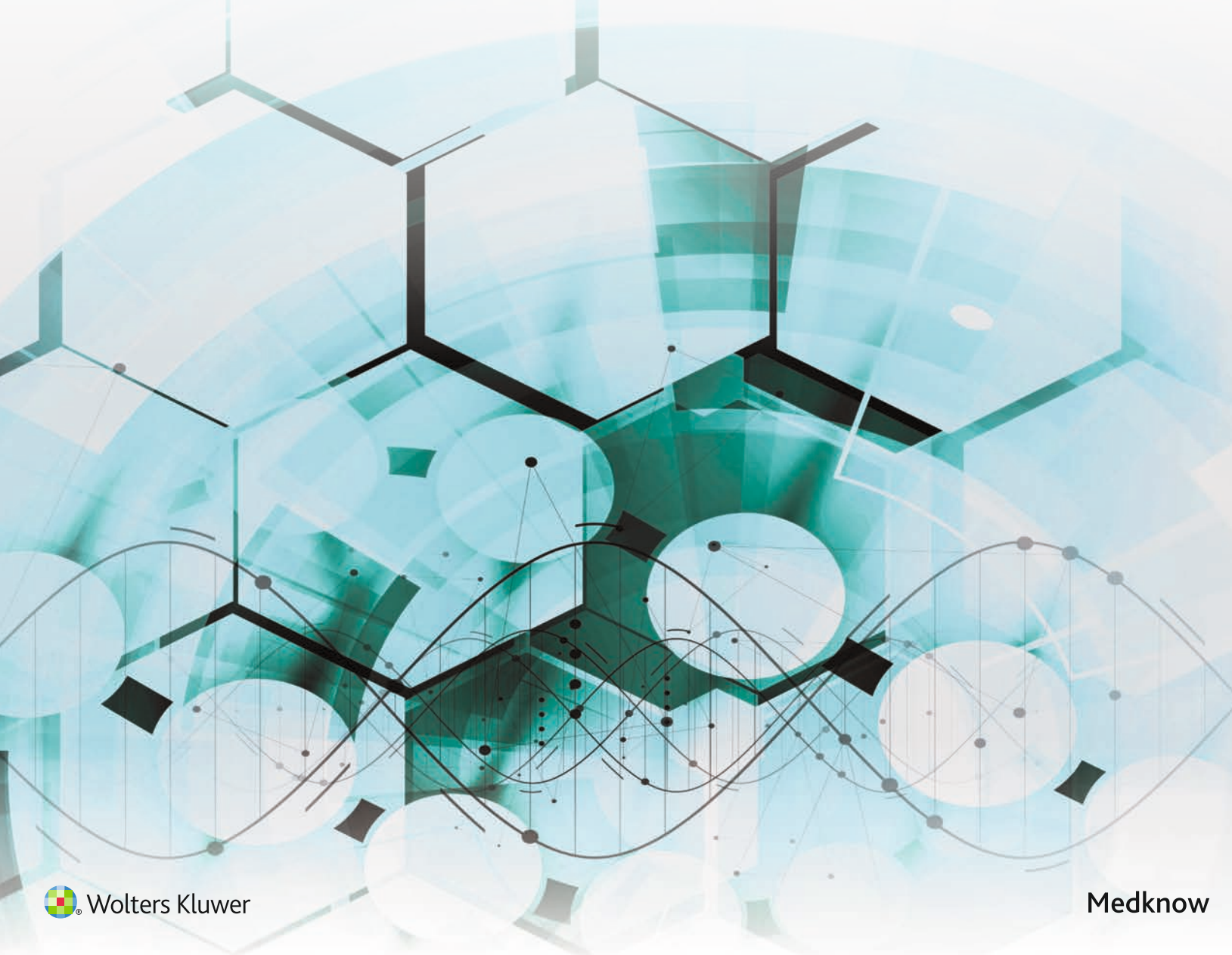

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Annals of Medical Science and Research

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Short Communication

The new competency-based medical education in India: Are we going to produce *elite quacks*?

New competency-based curriculum for medical graduates (competency-based medical education [CBME], 2019) brought about a paradigm shift, which was being planned about a decade back. In the year 2011, erstwhile Medical Council of India published a policy document - VISION-2015, where competency based medical education (CBME) and the term Indian Medical Graduate for a skilled basic doctor was first proposed.[1]

Unlike the old curriculum which focused on knowledge, was organized on systems and disciplines, was time based, and had a summative evaluation, competency-based learning emphasizes the skills required for medical practice. It focuses on learning the competencies needed in clinical practice and provides standards and framework for measuring performance.[2]

The thrust of the new curriculum attempts to make medical education in India more outcomes oriented. The new curriculum identifies certain skills, describes methods and contexts of teaching, and recognizes standardized measurement of competencies.

This outcome-oriented new UG curriculum is intended to provide the orientation and necessary skills for proper care of the patients. In particular, the curriculum provides for early clinical exposure, longitudinal care, and skill acquisition. The acquisition of skills is given utmost importance as an indispensable component of the learning process in medicine, and a detailed procedure of certification in certain essential skills is being prescribed, with the provision of the establishment of skill laboratories in a simulated and guided environment.[3]

It lists 412 topics for learning and 2949 outcomes to be mastered. It argues that broad competencies can be achieved in a phased manner while retaining the subject-wise character of the current organization of specialties and integrating teaching and learning across disciplines during the undergraduate course.[2]

However, a question has been raised regarding the relative importance given to the element of knowledge acquisition in comparison to that of skill development in the new curriculum. It is also said that the sections of cognitive components covered during the deliberation of basic disciplines are grossly undermined.[4]

The basic subjects delve into the fundamental premise of structure and functional homeostasis in human health and disease. A thorough and critical understanding of the subjects is not only essential to comprehend the pathophysiology of the diseases, to know clinical features and to frame therapeutic decision-making; the cognitive foundation of prospective academics in the field of medical science is also created.

As per Bloom's taxonomy, the domains of learning are cognitive, psychomotor, and affective, which broadly signify the knowledge, skill, and attitude components of learning, respectively. In the present curriculum, there is a substantial emphasis on the noncognitive domains with the provision of the foundation course, AETCOM module, early clinical exposure, and a battery of skill development components, but the cognitive domain is rather de-emphasized. In Bloom's original taxonomy (1956), the cognitive domain was further stratified into six levels such as *knowledge-comprehension-application-analysis-synthesis-evaluation*,[5,6] whereas the revised taxonomy (2001) espouses a slightly different one with an addition: *Remember-understand-apply-analyse-evaluate-create*,[7] wherein *create* is introduced as a higher order of cognitive goal. There are lengthy discussions and critical appraisal on these research areas of educational psychology in a large number of literature in India and abroad for the last several decades.[8] Without going into the details, it can be reasonably implied that intensive and extensive cognitive learning is needed to build up a strong foundation of basic subjects at the outset of UG tenure to develop appropriate acumen for analytical and evaluation proficiency in young enthusiastic minds. This initial preparedness will lead to the development of innovativeness and attitude for inquiry and research among medical graduates. However, relevant research in the field of medical education in our country is surprisingly sparse which indicates that the medical educationists of India are doing little groundwork and imposing certain overseas model to fit in.

In the current UG curriculum of medical graduates, the competence classification is leveled as *know-know how-show*

how-perform that indicates an apparent goal of performing ability and skill acquisition of the students.[2] At the lowest level of the pyramid is knowledge (knows), followed by competence (knows how), performance (shows how), and action (performs). This Miller's (1990) work-based assessment model for clinical competence is practically generalized as the basic model of UG medical education. This is in contradistinction to Bloom's taxonomy model of cognitive levels, as discussed earlier, which emphasizes the creative and innovative aspects of the learners. Thus, a relative overemphasis on the component of skill and competence than the knowledge component becomes the hallmark of the new CBME. In the absence of meaningful and significant works in this area of education research, it is not really a prudent proposition.

It is also well known that CBME focuses on immediate needs and is less focused on preparing learners with the flexibility needed for a more uncertain future and does not suit subject areas, where it is difficult to prescribe specific competencies or where new skills and new knowledge need to be rapidly accommodated. It also takes an objectivist approach to learning and does not suit developing a higher level, more abstract knowledge and skills requiring creativity, high-level problem-solving and decision-making, and critical thinking.[9] Knowledge-based learning is also essential for clinical practice.[10]

Another area in the present curriculum where there is an apprehension of potential downslide of the cognitive component is the introduction of too much objectivity in the student evaluation system. For example, the proposition of objectively structured practical examination (OSPE), objectively structured clinical examination (OSCE), and simulated experimentation in virtual platforms is said to substantially replace the conventional pattern of practical and clinical examinations. Practical teaching is one form of active learning or the process of having students engage in an activity that forces them to reflect on ideas and how they are using those ideas. Knowledge is gained through a cycle of hands-on experience with reflection guided to the conceptualization and then returning to the application. When complemented by self-assessment, the students' understanding and skills are further enhanced. Practical teaching is a student-focused learning rather than a teacher-centric deliberation that leads to increased student interest, attention, and knowledge retention. This facilitates better solutions to problems, increased mastery of conceptual reasoning, and better retention compared to learning alone.[11,12] The practice of conducting scientific investigation even in a small setup of UG laboratory leads to the acquisition of fundamental scientific concepts and is critical in nurturing a lifelong interest in science. It also provides opportunities to develop research skills crucial in science and medicine careers, including precision, accurate measurement, and the mastery of often delicate equipment. It also develops important transferable skills, such as teamwork, resilience, and analysis. Fundamentally, medical science is a practical discipline and, by undertaking good practical science at the UG level, one gains the proper scientific temper that might help the student to adopt a science-related occupation in the future.[13]

In conventional practice, the examinee has to perform and conduct the whole experimental procedure or clinical workout under the supervision of the examiner and draw the result and conclusion. However, in OSPE/OSCE setting, the whole experimentation, testing, and clinical examination is not done by the students during the practical examination. It is only a piecemeal portion of the whole experiment is prepared in a highly objective manner in front of an "informed observer," who may not always be qualified examiner personnel (i.e. non-teaching staffs or lab. technicians of the department etc). It has been observed by the seasoned examiners that, very soon after the onset of the examination the examinees come to know about the OSPE/OSCE items, memorize and mechanically follow suit in a rote manner. Accordingly, the desired objective of the examination is not fulfilled. As a consequence, there may be an adverse and detrimental effect on the practical, clinical, and experimental learning of the students, simply because the major proportion of the students intends to perform in the examination only. The students might lose interest in conducting experimental practical in regular classes, and may fail to learn proper clinical examination procedures. Poor physical examination skills are a threat to patient safety as the probability of diagnostic errors and oversights is increased. Sir William Osler told, *"The whole art of medicine is in observation… but to educate the eye to see, the ear to hear and the finger to feel takes time, and to make a beginning, to start a man on the right path, is all that you can do."*[14]

The age-old module of imparting practical teaching characterized by "causal inference from experiment and observation"[15] is largely ignored. It is well known that a good practical lesson cannot be replaced by a virtual session.[16] As Max Plank wrote, "Experiment is the only means of knowledge at our disposal. The rest is poetry, imagination."

Accordingly, there exists a reasonable apprehension that the cognitive foundation of the budding medicos will be liable to be compromised in the hype of skill training, too

much objectivity in assessment protocol, and lack of actual experimentation. The new system would produce more of elite quacks than scientific doctors.

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Review Article

The epidemiological and clinical features of monkeypox in human: Present global status and future management in Bangladesh

Md. Taimur Islam, Anas Bin Harun[1], Abdullah Al Bayazid[1], Shahnaz Sultana[2], Mirza Mienur Meher[3], Anup Kumar Talukder[4], Md. Golam Haider

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Abstract

A recent outbreak of the pandemic monkeypox has posed a deep concern to human health just following the devastating outbreak of COVID-19. The monkeypox-infected patient was detected in England on May 7, 2022. Here, we aimed to describe the epidemiology, pathogenesis, treatment, and diagnosis of monkeypox with the global responses to tackle this dreadful disease, particularly on how Bangladesh can deal with this disease having limited resources. To date, a total of 85,158 people are officially reported as monkeypox infected with 88 deaths. To combat this disease, various steps have been taken globally such as diagnosis of the suspected cases, vaccination programs, antiviral drug therapy, frequent reporting of the cases, restrictions on animal trade, quarantine of suspected people, isolation of infected patients, increase public awareness, and global collaboration. Moreover, we attempted to provide some guidelines to restrict this deadly disease in Bangladesh, highlighting the current challenges of this disease.

Keywords: Epidemiological and clinical features, future directions for Bangladesh, monkeypox, recent outbreak

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INTRODUCTION

A recently reemerged virus known as the monkeypox virus has attracted attention just as the globe is still attempting to mend after a catastrophic couple of years of the pandemic COVID-19. Initially, the monkeypox virus is only found in Central and Western Africa, but it is now being rapidly transmitted throughout Europe. Up until January 30, 2023, 85,158 instances from 107 countries have already been reported, with 88 deaths. Bangladesh has not yet reported any suspected or confirmed cases.[1]

Monkeypox virus is a zoonotic virus that causes monkeypox that exhibits common attributes of smallpox. The symptoms of monkeypox, predominantly the rashes, resemble the features of smallpox though clinically, monkeypox is less complex and severe than smallpox.[2] In

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1970, courses of efforts were made to eradicate smallpox and till then no monkeypox case was identified.[3] In most cases, smallpox and monkeypox produce almost the same symptoms that include 7–17 days of the incubation period, 1–4-day prodromal period, 14–28-day rash period, fever, malaise, headache, lesions on palm and sores, centrifugal lesion distribution, and hard deep with well-circumscribed lesion appearance, except lymphadenopathy which is distinct in monkeypox.[4,5]

As it has started to invade the countries one after another, Bangladesh is at high risk because of high population density (ca. 170 million people in 147,570 km^2), poor health-care systems, poverty, and the weak economy.[6] In addition, the people of our country are not properly informed and aware of the risks of the monkeypox virus. Therefore, this report aimed to focus to provide the basic layout of this virus and the disease and current scenario of monkeypox globally. Moreover, it provides some important recommendations and directions on how Bangladesh can tackle this dreadful disease.

ETIOLOGY AND TRANSMISSION

Monkeypox virus belongs to the genus of *Orthopoxvirus* of the family of *Poxviridae* under the kingdom of *Bamfordvirae*. Poxviruses are presented as brick shaped under an electron microscope. The virus genome consists of a linear double-stranded DNA, enclosed by a lipoprotein envelope. They are slightly larger than the others in the same family having 200–250 nm in length.[7,8] As of now, two inheritance clades of the virus have been detected: the Congo Basin (the Central African Clade) and the West African clade. The former clade is more frequent and responsible for transmission between human-to-human.[9] On the other hand, the West African clade represents a more favorable prognosis with a case fatality rate below 1%, whereas the Central African clade is more lethal, with up to 11% fatality rate among the unvaccinated people, mostly children. Usually, the recovery period takes up to 4 weeks leaving scars and impale skin colors.[9]

Monkeypox virus transmission is no different than the other viral transmission. Transmission can be a result of both human-to-human and animal-to-human contact. Any exposure to human or animal body fluids, respiratory droplets, or secretions from the lesion can cause possible direct or indirect transmission of the virus. Human-to-human transmission is now more frequent due to decreasing herd immunity, which was an unusual method earlier.[10]

EPIDEMIOLOGY

The first case of the monkeypox virus was detected in 1958. The virus was caught while monkeys from Singapore were being shipped to a research program in Denmark.[11] As there was no proven record for the monkeypox virus at that time, the virus identified in monkeys was as smallpox.[12] In 1970, when the virus was first isolated from a child's body in Congo, it was suspected to be smallpox.[3] Later, the monkeypox virus was isolated from primates, prairie dogs, rats, mice, monkeys, and humans.[9] Human monkeypox cases were predominantly recorded in the tropical countries of Africa but sporadically recorded in non-African countries. Predominantly, central and western African forests and rural areas were the center of the virus and a great threat due to indiscriminately hunting wild animals and collecting bushmeat, taking care of other monkeypox virus-infected patients and depriving of the smallpox vaccine.[13] Males were mostly infected at that time as they were used to hunt and handle wild animals traditionally.[14]

Over the years, as the number of cases was not much concerning, it never caught attention up until now.[9] Other than many tropical African countries, 53 human cases were confirmed in the United States of America (USA) in the year 2003. The occurrence took place when Giant Gambian rats were cohabitant with the Prairie dogs in the same household.[15] The direct exposure to the virus caused animals to human contact, resulting in rising cases in the USA. Until now, the Monkeypox virus was epidemic in the western African countries. Traveling from those tropical countries resulted in many suspected and confirmed cases worldwide. For instance, in 2018, one positive case was filled with a man traveling to Israel from Nigeria (a western African country).[15] Following that year, in 2019, another case was confirmed of a man traveling to Singapore from Nigeria.[16] In addition, in 2021, three members of a single family were infected with the disease while traveling from Nigeria to the United Kingdom.[17] In the following year, another traveler from Nigeria to Maryland in the USA was positive for the monkeypox virus.[18]

MONKEYPOX CASES AROUND THE WORLD

The first case of monkeypox has been detected in England on May 7, 2022. To date, more than 107 countries or territories have confirmed the occurrence of monkeypox in human. A total of 85,158 people are officially reported as monkeypox infected with 88 deaths as of January 30, 2023.[19] The highest number of monkeypox patients has been reported in the USA which sum up 30,109 with 28 deaths [Figure 1 and Table 1].[31]

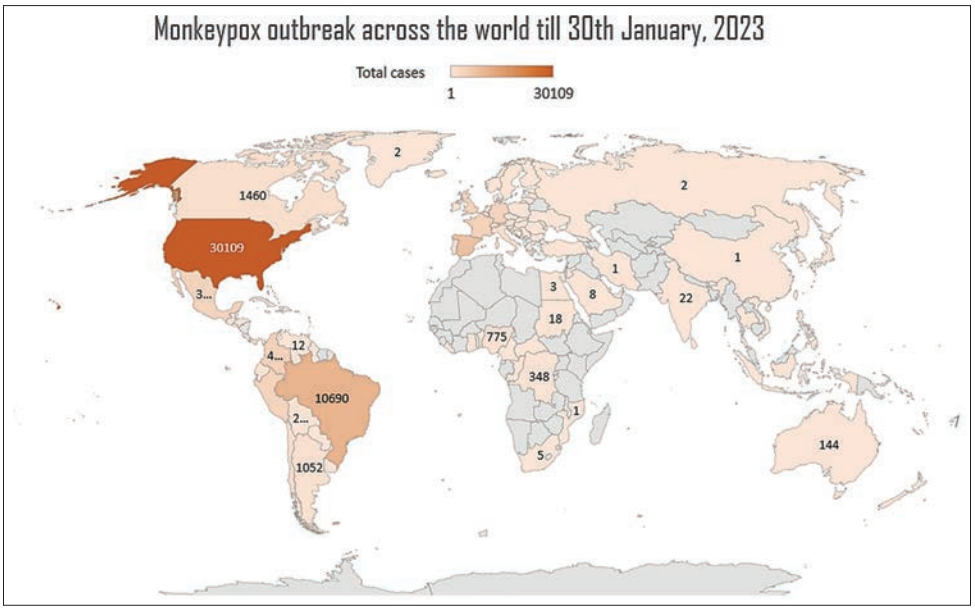

Figure 1: Global map of the monkeypox outbreak in 2022–2023. The map was produced in Microsoft Excel

PATHOGENESIS

When the viral transmission happens, either by human-to-human exposure or animal-to-human exposure, the virus enters the body. With replicating ability, the virus starts to replicate at an inoculation site and gradually invades the local lymph node. Along with the bloodstream, the first stage of viremia takes over other organs. The beginning state of viremia occurs within the initial incubation period persisting for nearly 1–2 weeks, max of 3 weeks. The second and further viremia leads to prodromal fever for 1–2 days. Progressively, lymphadenopathy may occur. Then, lesions start occurring in the oropharynx region and progress from the skin of upper extremities to the skin of lower extremities, while antibodies are detectable in blood serum [Figure 2].[19]

CLINICAL SIGNS

Correspondingly, the usual viral infection, monkeypox virus also presents with fever, body aches, headache, and weakness. In addition, lesions in the oropharynx and the extremities also occur. Lesions may also occur in palms and soles, gradually transforming them into hard scab-like structures. The lesion may localize in a particular area of the body or may spread all over the body surface.[2] After the incubation period of 7–14 days, lesions may appear in the form of macules, papules, vesicles, and then pustules. The size of lesions may vary from 2 mm to 10 mm in diameter. After 5–7 days scabs are formed as the pustules start to become dry. Once the lesions become hard, they start to fall off after 7–14 days. Commonly, the disease lasts for 3–4 weeks, and the patient does not cause any viral transmission after all the scabs are fallen off.[20]

Table 1: Timeline of first confirmed cases by country and number of positive cases and deaths (as of January 30, 2023)

1st confirmed case	Country	Number of cases	Number of deaths	References
May 7, 2022	England	3735	0	[32,33]
May 18, 2022	Spain	7514	3	[34]
	Portugal	950	0	[35]
	United States	30,109	28	[36]
May 19, 2022	Italy	995	0	[37]
	Canada	1460	0	[38]
	Sweden	257	0	[39]
May 20, 2022	Belgium	790	1	[40]
	Germany	3689	0	[41]
	France	4114	0	[42]
	Netherlands	1260	0	[43]
May 21, 2022	Switzerland	551	0	[44]
May 22, 2022	Austria	327	0	[45]
May 23, 2022	Denmark	192	0	[46]
May 24, 2022	Czech Republic		1	[47]
May 26, 2022	Finland	42	0	[49]
May 28, 2022	Mexico	3696	4	[50]
May 31, 2022	Norway	94	0	[51]
June 9, 2022	Brazil	10,690	15	[52]
June 20, 2022	Singapore	21	0	[53]
June 22, 2022	South Korea	4	0	[54]
June 23, 2022	South Africa	5	0	[55]
July, 2022	New Zealand	41	0	[56]
July 12, 2022	Russia	2	0	[57]
July 14, 2022	India	22	1	[58]
	Saudi Arabia	8	0	[59]
August 5, 2022	Cyprus	5	0	[60]
August 12, 2022	Honduras	13	0	[61]
August 16, 2022	Iran	1	0	[62]
August 19, 2022	Indonesia	1	0	[63]
September 6, 2022	Hong Kong	1	0	[64]
September 7, 2022	Egypt	3	0	[65]
September 16, 2022	China	1	0	[66]
October 3, 2022	Vietnam	2	0	[67]

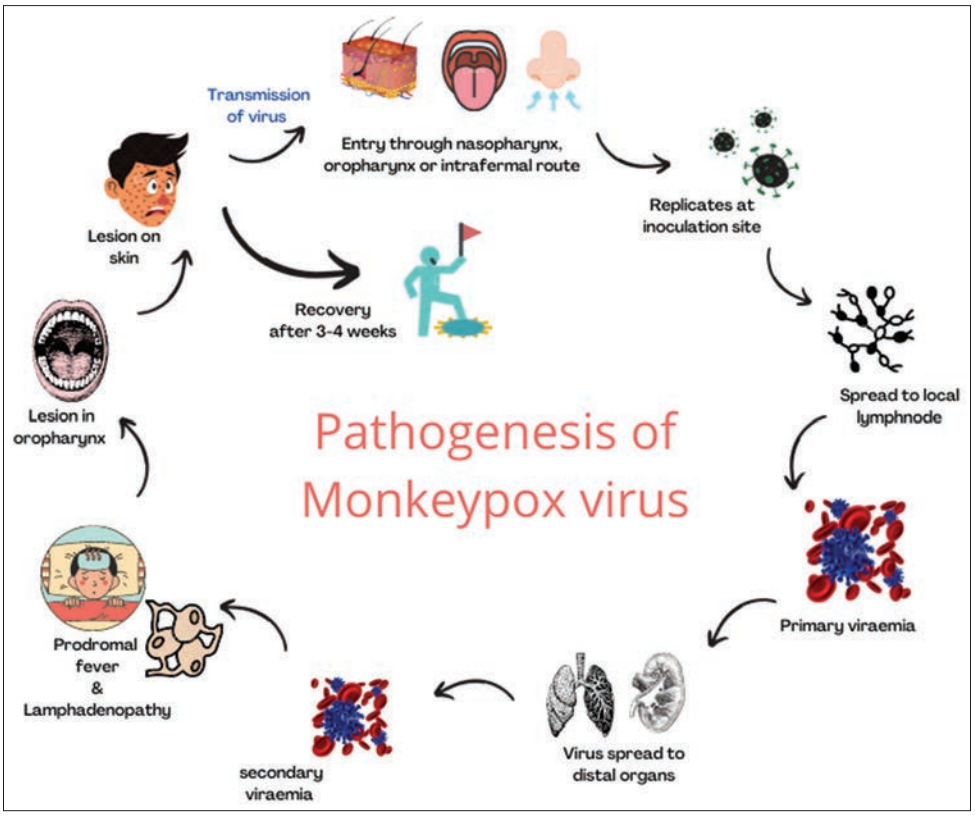

Figure 2: Pathogenesis of monkeypox virus after entering into the host body

In most cases, the after effect of the virus can lead to serious occurrences. Invasion in the lymphatic system can result in a weak immune system. Consequently, secondary bacterial infections may occur in some patients. The lesions result in persisting scarring on the skin. Lesions in the oropharynx, nasopharynx, and cornea can cause serious damage. There is a possibility of short sight, hypopigmentation, hyperpigmentation, or even blindness. Damage to the oropharynx mucous membrane can cause severe pain and impossible oral intake, resulting in malnutrition and dehydration and infection. Eventually, the infection can lead to sepsis and death.[21]

DIAGNOSIS

Diagnostic assays, for example, viral isolation in cultured cells or polymerase chain reaction of monkeypox DNA from a patient sample are essential in determining monkeypox. Exudate on a swab or crust specimens is used as samples. Viral DNA in lesion material is stable for a long time if kept in a relatively dark, cool environment.[2] Alternatively, tests such as electron microscopy visualization, immunohistochemistry staining for *Orthopoxvirus* antigens, and serum investigations for anti-orthopoxvirus immunoglobulin M (IgM) and immunoglobulin G can be sufficient diagnostic tools. Investigation of serum IgM level is more applicable to diagnose recent retrospective infections, including in individuals with prior vaccination.[22] However, they necessitate considerable technical skills and training, as well as a sophisticated laboratory. These laboratory tests are most effective when paired with clinical and epidemiological information, including a patient's vaccination history.[23-25]

TREATMENT

As of now, the monkeypox was not a concerning issue. As a result, there are no clinically established treatments for the disease. Like the other viral diseases, the monkeypox virus also requires a symptoms control treatment plan. Regardless of a proper treatment plan, some precautionary measures can be taken during the disease to intercept the severity of the outbreak. The first and most significant measure is in isolation. The patient should wear a mask, and the exposed areas should always be covered to prevent possible transmission. The infected individual should remain in isolation, wear a surgical mask, and keep lesions covered as much as reasonably possible until all lesion crusts have naturally fallen off and a new skin layer has formed.[2] As the virus is considered to have an upper-limit incubation period, patients should be closely monitored for 21 days from the day of possible exposure. Vaccinia

Vaccines can be used to break the chain of transmission and lower the severity of the disease. Afterward, a nonreplicating vaccine such as the Ankara vaccine is also recommended. According to the Centers for Disease Control and Prevention, vaccination within the 1st 4 days of exposure can arrest the possibility of the disease occurring, and severity may reduce if vaccination is performed within 14 days of exposure.[26] The availability of medical care and sufficient diagnosis tests can act as weapons against the previously neglected tropical disease.[9]

GLOBAL RESPONSE TO RECENT MONKEYPOX OUTBREAK

Despite the fact that researchers did not foresee the monkeypox outbreak turning into a pandemic like COVID-19, the current rise of cases has raised concerns. It is unconfirmed what is causing the outbreak; there is no evidence that the virus has mutated, the outbreak has not been linked to travel to Africa, and not all of those affected have had sex with men (MSM).[12] Given the rapidity of the outbreak and the lack of clarity about what is causing it, scientists' first target is to identify the sources of the cases and whether the virus has changed its properties. Thus, governments are prompted to increase surveillance of monkeypox to determine its current transmission levels and its projection. Over 100 suspected and confirmed cases are being investigated by public health authorities in Europe and North America.[12]

In terms of prevention and control, officials are now relying on precautionary measures such as adequate containment measures, frequent reporting of the cases, restrictions on animal trade, and global collaboration. The WHO is developing new immunization programs for countries and convening more meetings to provide member countries with further advice to tackle the situation. There are also vaccines and therapies available, prompting more governments to undertake immunization campaigns to tackle the soaring infection rate. Although smallpox was eradicated more than four decades ago, vaccine stocks have been kept on hand in case the disease resurfaces.[27]

The European Commission is proceeding with the centralized procurement of Tpoxx® (tecovirimat), an antiviral drug from Siga Technologies, and Imvanex® (Live Modified Vaccinia Virus Ankara), a smallpox and monkeypox vaccine from Bavarian Nordic, to be used off-label in response to monkeypox cases.[27] Because the number of smallpox vaccines accessible in Europe was unclear, EU officials are currently mapping the availability of Imvanex® stockpiles. On May 27th, the commission stated that Health Emergency Preparedness and response authority were coordinating steps and procuring drugs to combat monkeypox with member states and drug manufacturers [Table 2].[27] Another antiviral agent named cidofovir with the brand name Vistide was used against monkeypox in different countries. Different steps were taken by different countries to stop the spreading of monkeypox [Table 2].

BANGLADESH'S RESPONSE TO MONKEYPOX

Although no monkeypox cases have been reported in Bangladesh, the country has issued a health alert to prepare for any possible outbreaks of the disease. The directorate general of health services has issued an alert to all ports in Bangladesh, including land, air, and seaports, to conduct monitoring and screening of passengers to prevent the spread of monkeypox in the country.[36] The alert was also disseminated across the health department,

Table 2: Major steps taken by different countries against spreading of monkeypox

Country	Responses
United Kingdom	First to offer immunization Immunization of adults and medical personnel
Germany	Ordered 20,000 doses of Imnavex[68]
United States	Licensed Jynneos™ (an attenuated, live, nonreplicating smallpox and monkeypox vaccine) for the treatment[69] LGBT community advised to be cautious
Canada	National Microbiology Laboratory began accepting sampling Prepositioning the vaccination Imvamune® and therapeutics from the NESS around the country[70]
Australia	Activation of National Incident Centre to facilitate the national response AHPPC and CDNA have convened and will continue to meet to monitor the situation
United Arab Emirates	Increased safety precautions against the spreading of the virus and is investigating any suspicious cases Claimed to provide precise diagnostic mechanisms with a detailed handbook for surveillance, early disease identification, clinically infected patient management, and preventative measures
China	China CDC has developed an emergency response technical plan for monkeypox, stored monkeypox detection reagents, and trained provincial and municipal CDC experts in monkeypox nucleic acid PCR testing Stated that they have created nucleic acid test kits for monkeypox that can be easily mass-produced and distributed on the domestic market[71]
India	Advised avoiding direct contact with positive tested individuals and emphasized observing unusual symptoms, particularly in those with a travel history from monkeypox infected areas Proposed mandating international travellers to be quarantined for at least 2 weeks
Nepal	Supposedly increased border surveillance[34,35]

CDC: Centers for disease control, AHPPC: Australian Health Protection Principal Committee, CDNA: Communicable Diseases Network Australia, PCR: Polymerase chain reaction, LGBT: Lesbian, gay, bisexual and transgender, NESS: National Emergency Strategic Stockpile

including to the district civil surgeon. According to an advisor of the institute of epidemiology, disease control, and research (IEDCR), airports currently do not require anything other than thermal scanners.

The health professionals emphasized raising public awareness about the monkeypox virus. They also recommended patients seek medical attention if they experienced any symptoms and asked hospitals to gather patient samples and send them to the IEDCR. They urged livestock scientists to do a thorough investigation of various monkeypox-infected animals. The vice-chancellor of the Bangabandhu Sheikh Mujib Medical University recommends that infected individuals are isolated until the lesions crust.[37] Despite his belief that Bangladesh has made the essential preparations, the availability of smallpox vaccines and the course of action remain unclear.

FUTURE DIRECTIONS FOR BANGLADESH

Bangladesh, a biosecurity-vulnerable country, must be adequately equipped to combat disease outbreaks. Implementing the correct measures can help to easily restrict disease. The first line of defense should be to tackle the risk factors, some of which Bangladesh possesses. Therefore, the following initiatives should be taken to control the disease:

Pregnant women, children, immunocompromised individuals, and health personnel who do not have sufficient personal protective equipment are particularly susceptible.[12] Pregnant women and youngsters should be given special attention. Nutritional awareness should be increased to strengthen the immune system.

If required, international travelers should be quarantined. Since homosexuality is illegal in Bangladesh,[28] law enforcement agencies should carefully monitor these communities and prevent them from coming out. In any case, public health guidance for them should be provided to support the development of risk communication and community engagement messaging.

Because monkeypox lesions commonly appear on the skin of many or all parts of the body, as well as in the mouth, there is a high risk of further virus transmission through close physical contact within families or with sexual partners.[12] As a result, physical contact should be restricted. The virus is transmitted through inhalation, and virus particles can survive for up to 1 week on clothing, bedding, and surfaces. As in the COVID-19 scenario, the use of a mask should be recommended.

Animal bites and scratches from infected animals have the potential to transmit the virus as well.[29] The presence of dysphagia, hypoxemia, and mouth sores was strongly linked with a serious infection in a bivariate study. However, there were no significant risk factors in multivariate analyses.[29]

Isolation of a diseased patient can take place in a health-care institution or at home, as long as the infected person can be isolated and properly cared for. Large gatherings may provide an ideal setting for the spread of the monkeypox virus because they involve close, lengthy, and frequent encounters among people, which can expose participants to lesions, body fluids, respiratory droplets, and contaminated surfaces.

Bangladesh is more vulnerable due to its large population. While the precise mechanisms of transmission of the current monkeypox outbreak are still being investigated, the basic precautionary measures indicated against COVID-19 are also expected to protect against monkeypox virus transmission.

Monkeypox surveillance, case investigation, and contact tracing are crucial for rapidly identifying cases and clusters to give the best clinical care; isolating individuals to avoid further transmission; identifying and managing close contacts; and tailoring effective control and preventative strategies.

Vaccination against smallpox has been demonstrated to be cross-protective against monkeypox, with up to 85% efficiency, according to health authorities around the world.[30] However, vaccination needs to be confined to very specific cases and groups because of the transmissibility and risk of the virus not being comparable to COVID-19, and side effects have yet to be fully discovered[27] as more than 40 years have passed since smallpox eradication, vaccination stocks may need to be refreshed as well. Persons with herpes and cytomegalovirus are treating with antiviral medications such as acyclovir and valacyclovir in Bangladesh. These antiviral agents are available in Bangladesh. Although it is unknown if they are helpful for monkeypox in humans, *in vitro* and animal research demonstrate their effectiveness.

CONCLUSION

The monkeypox virus, which can infect humans, causes the viral zoonosis known as monkeypox. Its symptoms resemble those of those who formerly had smallpox. Numerous animal species have been proven to be affected by the monkeypox virus. When a person comes into touch

with infected people, animals, or things, the monkeypox virus can be transmitted. It is still not possible to treat a monkeypox virus infection safely and effectively. However, the symptoms may dictate the course of the treatment. In order to combat this illness, a variety of measures have been implemented worldwide, including the diagnosis of suspected cases, vaccination campaigns, antiviral drug therapy, routine case reporting, restrictions on the trade in animals, quarantines of suspects, isolation of infected patients, increased public awareness, international cooperation, and others. Bangladesh, a country with poor biosecurity, must be well-equipped to handle disease epidemics. Despite the fact that there have been no cases of monkeypox found in Bangladesh, the country has warned all ports there, including those on land, in the air, and on the sea, to monitor and screen travelers to prevent the disease from spreading there. Along with this, the government should consider hastening the development of a vaccine plant that will be helpful for all future goals connected to vaccines. International travelers had to stay inside for a few days as well. In addition, the prevention of monkeypox depends on the early detection of likely cases, social isolation, maintaining personal hygiene, and increasing public knowledge.

Author contribution

All authors contributed to the data collection and drafting of the manuscript. MTI conceived the idea, coordinated, critically edited, and revised the manuscript. The final draft was approved by all authors.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Screening of VHL mutation in different types of kidney cancer in patients of West Bengal (India)

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Abstract

Introduction: The purpose of this study was to screen the patients of West Bengal (India) with different types of renal cancer to see the presence of von Hippel–Lindau (VHL) gene mutations.

Materials and Methods: This prospective study included 25 patients with renal cancer operated on between December 2019 and January 2022. Tumor tissue and adjacent normal tissue samples were taken and subjected to genomic DNA isolation, polymerase chain reaction, DNA sequencing, and identification of polymorphism in renal cell carcinoma (RCC) patients by comparing with a database using "ENSEMBL" (genome browser) followed by the role of identified variants in disease-causing using different software.

Results: After analysis, we identified six exonic and one intronic variant in the VHL gene. rs34661876 A>G, AG genotype in intron 2–3 has increased the risk of RCC against the odd 6.729 times ($P = 0.0041$). It is present in 17 out of 25 case samples. rs1642742 G>A, AA genotype in exon 3 has increased the risk of RCC against the odd 22.167 times ($P = 0.0001$). It is present in 14 out of 25 case samples. The effect of these Single nucleotide polymorphism SNPs/mutations on VHL function were predicted by various bioinformatics software and it was found that rs1399097617 C>T, rs5030830 T>C, and rs1553620326 G>C are disease-causing.

Conclusion: If any of the above-mentioned variants are detected in RCC patients, then they will be benefited from the agents that modulate the VHL-hypoxia-inducible factor pathway and will help in developing new strategies for the management of RCC.

Keywords: Renal cell carcinoma, screening, von Hippel–Lindau

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INTRODUCTION

Renal cell carcinoma (RCC) is one of the most lethal common urological cancer and it accounts for 2%–3% of all adult malignancies.[1] In 2022, approximately 79,000 cases of RCC diagnosed in the United States, and 13920 patients die of the disease.[1] However, in the Asian region, the incidence of RCC is lower, especially in India, probably due to a lack of reporting.[2] The ratio of RCC in male: female in United States is about 1.8:1.[1] Whereas, in the Indian population male: female ratio is 4:1.[3-5] Although data from a developing countries (like from India) are limited, as per the SEER database, almost 50% patients with RCC present in the age group between 55 and 75 years and the median age at presentation is

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64 years.[6] Only 2%–3% of RCC are proven to be familial and rest are believed to be sporadic.[7]

Tobacco smoking, obesity, hypertension, and chronic renal failure are few common risk factors for RCC.[7-9]

RCC originates from the tubular structures of the kidney. There are several subtypes of RCC of which clear cell RCC (ccRCC) (70%–80%) is most common, followed by papillary RCC (10%–15%), chromophobe RCC (3%–5%), collecting duct carcinoma (<1%), renal medullary carcinoma (rare), unclassified RCC (1%–3%), and multilocular cystic ccRCC (uncommon).[10]

Within the past several years, as the understanding of the molecular biology of RCC is improved, new molecularly targeted agents for treating RCC have emerged. One crucial finding has been the discovery of the von Hippel–Lindau gene (VHL) and its importance in regulating the hypoxia pathway through the hypoxia-inducible factors (HIFs).[11]

The VHL gene is located at the 3p25.3 locus in the human genome. It is a tumor suppressor gene of 639 coding nucleotides divided into three exons. A tumor suppressor gene is one in which both copies of the gene must be disabled for cancer to develop. Seventy percent of patients will have a mutation of one VHL allele. Tumors do not form if one copy of the VHL gene is producing functional VHL protein. During the lifetime of a person, if a mutation occurs in the second copy of the VHL gene, the cell will have no working copies of the gene and will not produce functional VHL protein. A lack of this protein allows tumors characteristic of VHL syndrome to develop.[12]

VHL disease is an autosomal dominant syndrome manifesting with cerebellar and retinal hemangioblastomas, cysts of the pancreas, kidney, and epididymis, epididymal cystadenoma, pheochromocytoma, and ccRCC. It is found in all ethnic groups, both sexes are affected, and it has an incidence ranging from 1 in 30,000 to 1 in 50,000 individuals. It has more than 95% penetrance by the age of 65 years in affected individuals.[13]

VHL is affected in more than 90% of the ccRCC cases, either by allelic deletion, promoter methylation (20%), or mutations (70%–80%). The inactivation of VHL has been found to be a critical point in the initiation of tumor formation and is the major aspect of this study in the context of ccRCC. In this disease, mutations are classified depending on their type: frameshift and nonsense mutations that most likely abrogate VHL protein (pVHL) functions, and missense mutations whose effects can range from no or little impact to high destabilization of pVHL. The pVHL structure is divided in two major binding regions. The β-sheet is known to bear the HIF1/2α binding domains and the α-helical domain is responsible for EloB/C interaction [Figure 1]. Current knowledge suggests that mutations and transcriptional silencing of VHL in renal epithelial cells cause loss or modulation of cellular functions operated by the wild-type pVHL.[14-17] It is not clear by which mechanism, pVHL modulates the expression of target genes leading to ccRCC. Accumulated evidence suggests that pVHL is involved in targeted protein degradation and control of angiogenesis,[14-17] and there is evidence that pVHL is implicated in the regulation of extracellular pH,[18] formation of extracellular matrix,[19] and cell cycle control.[14]

Recently introduced targeted agents that modulate this VHL–HIF pathway include the US Food and Drug Administration-approved multitargeted tyrosine kinase inhibitors sunitinib and sorafenib and the mammalian target of rapamycin inhibitor temsirolimus. These agents have shown superiority to previous cytokine therapies and are now part of the arsenal used in the standard treatment of RCC.

MATERIALS AND METHODS

The study was conducted in a Tertiary Care Hospital in West Bengal (India) from December 2019 to January 2022. The present study protocol was reviewed and approved by the institutional ethical committee. Patients, who have highly suspected or tissue diagnosis proven RCC and willing to take part in this study, were included in the study. Those patients who were unwilling to take part in this study and those patients whose histopathological examination proved to be benign diseases were excluded from the study. Informed consent was obtained by all participants when they were enrolled in the study.

This prospective observational study recruited 25 patients who underwent surgery for RCC. The demographic characteristics of the patients are given in Table 1. Tumor tissue and adjacent normal tissue were collected and processed in the following sequence:

Genomic DNA isolation → polymerase chain reaction (PCR) → DNA sequencing → Polymorphism analysis → Genotype analysis of detected variants → Role of detected variants disease-causing using software → Role of alterations in protein structure and function → Analysis of the data.

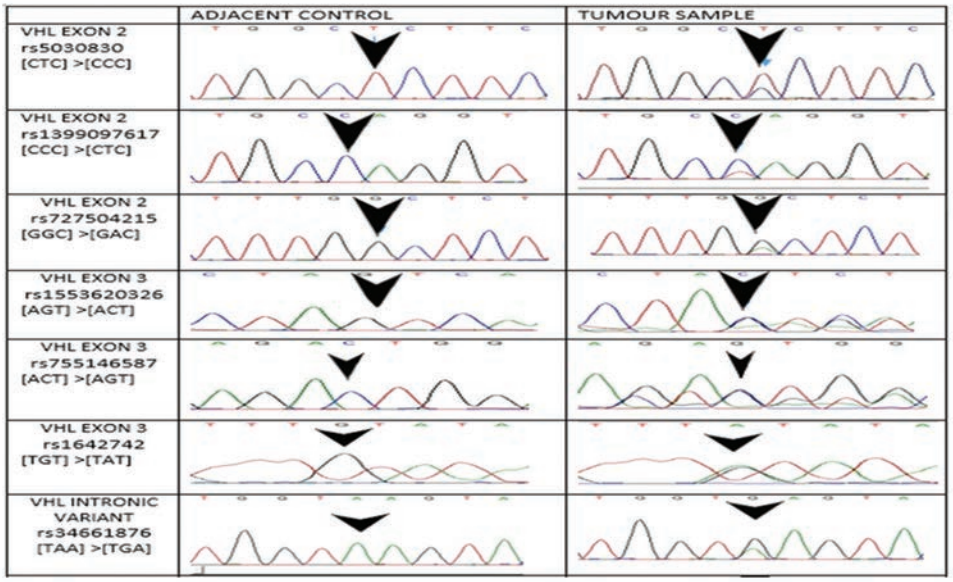

Figure 1: Sequencing chromatogram results of variants of VHL gene. VHL: von Hippel–Lindau

Genomic DNA isolation

Genomic DNA was extracted from tissue samples using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany), according to the manufacturer's protocols. DNA quantity was measured using the Nanodrop 1000 spectrophotometer. The OD range 260/280 good quality DNA should be 1.7–2. If a clear band is obtained quality of the DNA is good.

von Hippel–Lindau mutation screening

The entire coding region, exon–intron boundaries of VHL gene were amplified by PCR using specific primers [Table 2]. The primers were designed using integrated DNA technologies and primer 3 is a program web version 4.0.0 released under open-source license(s) (available from: http://primer3.ut.ee/).

Polymerase chain reaction

PCR reaction mixture contained 50 ng genomic DNA, 0.4 mM of forward and reverse primer, 0.2 mM of dNTP mix (Invitrogen Carlsbad, CA, USA), 1.5 mM MgCl2, 1PCR, buffer, and 2.5 Unit Taq polymerase (Invitrogen) and 4% Dimethyl sulfoxide (DMSO) was used. A thermocycler was applied to carry out PCR.

DNA sequencing

Direct sequencing of the DNA fragments containing DNA mutations was performed using the same primer sets used for PCR amplification. Sanger sequencing was performed using an automated DNA capillary sequencer (Model 3500; Applied Biosystems).

Determination of predicted functional significance of genetic alterations using *in silico* analysis

After sequencing, data analysis was undertaken to determine if there were any variants present. The sequencing data of the cancer group were compared with database (ENSEMBL).

Table 1: Demographic and clinical characteristics of participants in this study

Characteristics	Number of cases
Mean age at diagnosis (years)	
Male	51
Female	55
Gender	
Male	15
Female	10
Stage at diagnosis	
I	9
II	12
III	4
IV	0
Location	
Right	9
Left	16
Smoking status	
Smoker	17
Nonsmoker	8
Drinking habit	
Alcoholic	3
Nonalcoholic	22
Obesity	
Yes	7
No	18

Table 2: List of von Hippel-Lindau primers used in this study

VHL exon	Primers
Exon 1	Forward: 5'-GAGGTCAAGGCTGCAGTGAG-3'
	Reverse: 5'-GCTTCAGACCGTGCTATCGT-3'
Exon 2	Forward: 5'-TTAGCCAGGACGGTCTTGAT-3'
	Reverse: 5'-TGGATAACGTGCCTGACATC-3'
Exon 3	Forward: 5'-CAGAGGCATGAACACCATGA-3'
	Reverse: 5'-TATGCTGCAATTCCCACTGA-3'

VHL: von Hippel-Lindau

All the sequences containing the mutation were evaluated for their potential pathogenicity using the following algorithms: PolyPhen-2, SIFT, PROVEAN, FATHMM, SNPs and GO, I-MUTANT, Mutation Taster, and Regulation Spotter. To find the protein stability and the scores for free energy alterations for changing the single site mutation, the sequences were submitted to Project Have yOur Protein Explained (HOPE; http://www.cmbi.ru.nl/hope/home) for prediction of structural variation between wild and mutant type amino acids, which provides the three-dimensional structural visualization of desire proteins.

RESULTS

Genomic DNA isolation

The DNA concentration in the samples ranges from 104.63 to 315.56 ng/ul. The 260/280 ratios were in most of the DNA samples above 1.7, implying the DNA quality is good.

The DNA, was further checked for quality and run on 0.7% agarose gel, was found to be good in quality. There were no smears under the DNA bands, indicating that the DNA is not degraded.

Polymerase chain reaction

There was a single band of PCR product that means PCR products are pure and no contamination is observed.

Polymorphism analysis

We compared the DNA sequences from normal and tumor tissues from RCC patients to investigate somatic gene alteration. The results of sequencing are presented in Figure 1. We genotyped the sequence of three exons of the VHL gene and found seven variants. Among these variants, six are exonic and one is intronic.

We have found three missense variant mutations in exon 2 of VHL gene which are rs727504215 G>A, rs1399097617 C>T, and rs5030830 T>C. All of them are registered in the HGMD database (HGMD IDs are HM971481, CM941378, and CM961426, respectively) and COSMIC DB database (IDs are COSV56543268, COSV56548381 and COSV56544274, respectively). We have also identified two mutations in the coding region rs1553620326 G>C and rs755146587 C>G and one missense variant rs1642742 G>A in the noncoding region of exon 3. We have also identified an intronic variant rs34661876 A>G in intron 2.

Genotype and risk association

The genotypic data of the mentioned mutations/polymorphisms are provided in Tables 3a and 3b. We have performed Fisher's exact test to calculate the odds ratio, relative risk ratio, and 95% confidence interval (CI) for each heterozygous and homozygous recessive genotype taking the homozygous dominant genotype as a reference. $P < 0.02$ is considered to be statistically significant after Bonferroni's correction.

We have found the presence of rs34661876 A>G in intron 2–3 of the VHL gene. We have found this polymorphism in our case samples where minor allele "G" has shown the elevated risk of RCC against the odd 6.729 times (95% CI – 1.938–23.364, relative risk – 2.698, relative risk of CI − 1.300–5.599, $P = 0.0041$).

We have detected rs1642742 G>A in the noncoding region of exon 3 of the VHL gene. The heterozygous genotype GA is found among five case samples with respect to four control samples with an odds ratio of 3.958 (95% CI – 0.7961–19.682, relative risk – 1.71, and relative risk of CI – 0.7972–3.668 but the $P = 0.1108$) is not statistically significant. On the other hand, the homozygous recessive genotype AA is found among 14 case samples in contrast to two control samples with an odds ratio of 22.167 (95% CI – 3.878–126.71, relative risk –6.08, and relative risk of CI – 1.632–22.653, where the $P \leq 0.0001$) is statistically significant.

In silico analyses of identified variants

We used six different *in silico* nonsynonymous SNP prediction tools (PolyPhen-2, SIFT, PROVEAN, FATHMM, SNPs and GO and I-MUTANT) to find out whether the identified variants can significantly alter the structure or function of VHL protein or not. Each of these programs uses different algorithms to infer the deleterious effect of polymorphism or mutation. We have considered any given variant as "damaging" when any two of these detect a variant as damaging or having a deleterious effects. The summary of the results of the analyses is provided in Tables 4a and 4b.

rs1399097617 C>T, rs5030830 T>C, rs1553620326 G>C, and rs755146587 C>G are disease causing [explained in Table 4a]. rs1399097617 C>T, rs5030830 T>C, rs1553620326 G>C, and rs755146587 C>G deleterious and damaging [explained in Table 4b].

Prediction of Mutation Taster and Regulation Spotter

Regulation Spotter and Mutation Taster identified rs1399097617 C>T, rs5030830 T>C, and rs1553620326 G>C disease-causing [Table 5].

Protein modeling

In silico analysis of the structural effect of point mutation on human von Hippel–Lindau protein

Project HOPE server revealed that the mutant residues of V170 L (rs1553620326) the mutant residue is bigger

Table 3a: Distribution of von Hippel-Lindau risk variants among the patient cancer tissue (*n*=25) and adjacent control tissue samples (*n*=25)

Variants	Type	Location	Amino acid change	Base position (GRCh38.p13)	Genotype	Controls (*n*=25)	Case (*n*=25)	OR	95% CI	*P*	RR	CI of RR
rs34661876	Intronic	Intron 2-3	N.A	chr3: 10146679	AA	19	8	Reference as wild type				
A>G	variant	(ENST000002564743)			AG	6	17	6.729	1.938-23.364	0.0041	2.698	1.300-5.599
					GG	0	0					
rs727504215	Missense	Exon 2	W117C	chr3: 10146524	GG	25	24					
G>A	variant	(ENST000002564743)			GA	0	1					
					AA	0	0					
rs1399097617	Missense	Exon 2	P154L	chr3: 10146634	CC	25	24					
C>T	variant	(ENST000002564743)			CT	0	1					
					TT	0	0					
rs5030830	Missense	Exon 2	L118P	chr3:	TT	25	24					
T>C	variant	(ENST000002564743)		3:10146526	TC	0	1					
					CC	0	0					

CI: Confidence interval, OR: Odds ratio, RR: Relative risk

Table 3b: Distribution of von Hippel-Lindau risk variants among the patient cancer tissue (*n*=25) and adjacent control tissue samples (*n*=25)

Variants	Type	Location	Amino acid change	Base position (GRCh38.p13)	Genotype	Controls (*n*=25)	Case (*n*=25)	OR	95% CI	*P*	RR	CI of RR
rs1553620326	Missense	Exon 3	V170L	chr3: 10149831	GG	25	24					
G>C	variant	(ENST000002564743)			GC	0	1					
					CC	0	0					
rs755146587	Missense	Exon 3	L178V	chr 3: 10149855	CC	25	24					
C>G	variant	(ENST000002564743)			CG	0	1					
					GG	0	0					
rs1642742	Missense	Exon 3	N.A	chr3: 10150259	GG	19	6	Reference as wild type				
G>A	variant	(ENST000002564743)			GA	4	5	3.958	0.7961-19.682	0.1108	1.71	0.7972-3.668
					AA	2	14	22.167	3.878-126.71	<0.0001	6.08	1.632-22.653

CI: Confidence interval, OR: Odds ratio, RR: Relative risk

Table 4a: Predicted outcome of the polymorphisms found in von Hippel–Lindau gene using bioinformatics tools SNP and GO and I-mutant

Variants	Type	Amino acid change	SNPs and GO		I-Mutant				
			Prediction	Score	SVM2 prediction effect	RI	DDG value prediction	SVM3 prediction effect	RI
rs34661876 A>G	Intronic variant	N.A	-	-	-	-	-	-	-
rs727504215 G>A	Missense variant	W117C	-	-	-	-	-	-	-
rs1399097617 C>T	Missense variant	P154L	Disease	8	Decrease	7	−0.65	Large decrease	2
rs5030830 T>C	Missense variant	L118P	Disease	10	Decrease	6	−1.69	Large decrease	3
rs1553620326 G>C	Missense variant	V170L	Disease	6	Decrease	8	−1.31	Large decrease	4
rs755146587 C>G	Missense variant	L178V	Disease	6	Decrease	8	−2.00	Large decrease	7
rs1642742 G>A	Missense variant	N.A	-	-	-	-	–	-	-

than the wild-type residue. The residue is located on the surface of the protein, mutation of this residue can disturb interactions with other molecules or other parts of the protein [Figure 2a]. In the case of L178V (rs755146587), the mutant residue is smaller than the wild-type residue. This will cause a possible loss of external interactions [Figure 2b].

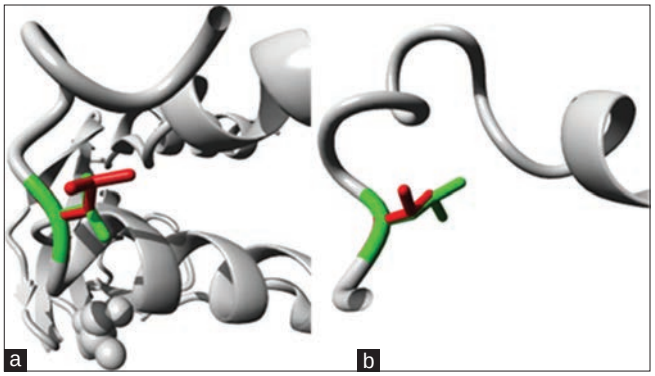

Figure 2: Structural alteration of SNPs. (a) V170L (b) L178V. The protein is colored gray, and the side chains of both the wild-type and the mutant residue are shown and colored green and red, respectively

DISCUSSION

Demographic study identified that in West Bengal, the most common age of presentation of RCC is 51–60 years and the mean age of presentation is 56.88 years. Whereas in developing countries (as per SEER database), the common age of presentation is 55–75 years and the mean age of presentation is 64 years.[6] In West Bengal, the male: female ratio of RCC is 1.5:1, whereas in United States, this ratio is 1.8:1.[1] Tobacco addiction (mainly in the form of smoking) is more commonly present in the RCC patients of West Bengal (17 out of 25 patients, 68%). In West Bengal, among the RCC patients, ccRCC is most commonly found (24 out of 25 patients, 96%), followed by papillary RCC being found in 4% of cases. While no other subtypes (such as chromophobe) are being found, which might be due to the small number of patients studied. Most of the patients diagnosed to have RCC in Stage I and Stage II (21 out of 25 patients, 84% cases) of their disease.

After analysis, we identified six exonic (rs727504215 G>A, rs1399097617 C>T, rs5030830 T>C, rs1553620326 G>C, rs755146587 C>G, and rs1642742 G>A) and 1 intronic (rs34661876 A>G) variant in VHL gene. Genotype and risk analysis identified that rs34661876 A>G, AG genotype in intron 2–3 has increased the risk of RCC against the odd 6.729 times (95% CI − 1.938–23.364, relative risk − 2.698, relative risk of CI − 1.300–5.599, $P = 0.0041$). It is present in 17 out of 25 case samples. Indicating that if the above-mentioned variant (rs34661876 A>G; AG genotype) is found in VHL gene, so that if it is found in any person/suspected patient/relative of a diagnosed case of RCC then the probability of having RCC in that person/suspected patient/relative will increase by 2.69 times, so regular follow-up of person will be required. rs1642742 G>A, AA genotype in exon 3 has increased the risk of RCC against the odd 22.167 times (95% CI − 3.878–126.71, relative risk − 6.08, relative risk of CI − 1.632–22.653, $P = 0.0001$). It is present in 14 out of 25 case samples. Indicating that if the above-mentioned variant (rs1642742 G>A, AA genotype) is found in VHL gene, so that if it is found in any person/suspected patient/relative of a diagnosed case of RCC then the probability of having RCC in that person/suspected patient/relative will increase by 6.08 times, so regular follow-up of person will be required. The effect of these SNPs/mutations on VHL function are predicted by various bioinformatics software (PolyPhen-2, SIFT, PROVEAN, FATHMM, SNPs and GO, I-MUTANT, Mutation Taster and Regulation Spotter) and is found that rs1399097617 C>T, rs5030830 T>C, and rs1553620326 G>C disease-causing. A statistically significantly increased RCC risk was found for individuals that carry genotypes with at least one variant allele for the rs34661876 A>G SNP. rs1642742 G>A is a more sensitive risk factor for sporadic RCC.

Disruptions in the VHL tumor-suppressor gene are thought to play a role in the constitutive activation of HIFs, as regulated in part by HIF1A, which may lead to carcinogenesis.[20] As the frequency of mutation is

Table 4b: Predicted outcome of the polymorphisms found in von Hippel-Lindau gene using bioinformatics tools Polyphen-2, SIFT, PROVEAN and FATHMM

Variants	Type	Amino acid change	Polyphen-2				SIFT		PROVEAN		FATHMM	
			HumDiv score	HumDiv prediction	HumVar score	HumVar prediction	Prediction	Score	Prediction	Score	Prediction	Score
rs34661876 A>G	Intronic variant	N.A	-	-	-		-	-	-	-	-	-
rs727504215 G>A	Missense variant	W117	-	-	-		-	-	-	-	-	-
rs1399097617 C>T	Missense variant	P154L	1	Probably damaging	1	Probably damaging	Affect protein function	0	Deleterious	−7.947	Cancer	−7.19
rs5030830 T>C	Missense variant	L118P	1	Probably damaging	1	Probably damaging	Affect protein function	0	Deleterious	−4.683	Cancer	−7.24
rs1553620326 G>C	Missense variant	V170L	0.9	possibly damaging	0.594	possibly damaging	Affect protein function	0	Neutral	−1.967	Cancer	−6.97
rs755146587 C>G	Missense variant	L178V	0.994	possibly damaging	0.984	possibly damaging	Affect protein function	0	Neutral	−2.467	Cancer	−7.11
rs1642742 G>A	Missense variant	N.A.	-	-	-		-	-	-	-	-	-

Table 5: Predicted outcome of the polymorphisms found in von Hippel-Lindau gene using bioinformatics tools Mutation Taster and Regulation Spotter

Variants	Type	Location: VHL (ENST000002564743)	Base position (GRCh38.p13)	Amino acid change	Mutation Taster			Regulation Spotter		
					Prediction	Model	Probability	Status	Model	Score
rs34661876 A>G	Intronic variant	Intron 2-3	chr3: 10146679	N.A	Polymorphism	without_aae	0.985	Likely effect nonfunctional region	Extratranscriptic	11.92
rs727504215 G>A	Missense variant	Exon 2	chr3: 10146524	W117	Disease causing	complex_ aae	1	Likely effect nonfunctional region	Extratranscriptic	21.02
rs1399097617 C>T	Missense variant	Exon 2	chr3: 10146634	P154L	Disease causing	simple_aae	1	Disease causing	Extratranscriptic	20.95
rs5030830 T>C	Missense variant	Exon 2	chr3: 3:10146526	L118P	Disease causing	simple_aae	0.99	Disease causing	Extratranscriptic	20.68
rs1553620326 G>C	Missense variant	Exon 3	chr3: 10149831	V170L	Disease causing	simple_aae	0.99	Disease causing	Extratranscriptic	20.44
rs755146587 C>G	Missense variant	Exon 3	chr 3: 10149855	L178V	Disease-causing	simple_aae	0.99	Likely effect nonfunctional region	Extratranscriptic	17.76
rs1642742 G>A	Missense variant	Exon 3	chr3: 10150259	N.A	Polymorphism	without_aae	0.99	Known variant polymorphism	Extratranscriptic	8.66

VHL: von Hippel-Lindau

very low in comparison to polymorphisms within a population (<1%), we cannot deduce any statistical significance by performing any suitable statistical method. Hence, a genotypic association study is not possible on this occasion. However, we have shown how the amino acid alterations are potentially disturbing the natural 3D conformation as well the functionality of the wild-type VHL protein with the help of several *in silico* analysis.

CONCLUSION

In our study, we examined the association of VHL gene polymorphisms with RCC in patients from West Bengal. By comparing the DNA from normal and tumor tissues, six exonic variants and one intronic polymorphism were identified. The heterozygous genotype AG of rs34661876 A>G is found in 17 out of 25 samples with a $P = 0.004$. The homozygous recessive genotype AA of rs1642742 G>A is found among 14 case samples. Hence, these two SNPs are significantly associated with RCC.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Ex vivo vaporization performance study of human prostate tissue using in-house designed thulium fiber laser

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Abstract

Introduction: Laser technologies including thulium, Holmium: Yttrium aluminum garnet (Ho: YAG), Potassium-titanyl-phosphate and diode laser have been explored in recent years for the treatment of benign prostatic hyperplasia. These thermal modalities impart their effect through ablative and coagulative mechanisms of action. Although Ho: YAG laser is a gold standard clinical tool in urology, its properties are not sufficient for cutting or coagulation of prostatic tissue. Thulium: YAG laser is a promising alternative laser but with limitations. The recent technological advancements in thulium fiber laser (TFL) provide various advantages along with a compact system for urosurgical applications. This paper depicts the work done in initial validation of an in-house designed TFL in *ex vivo* vaporization and vaporesection of human prostatic tissue. Comparison of its ablation rate and coagulation zone was done with the existing laser systems.

Methods: An in-house designed TFL having maximum continuous wave (CW) power level of 70 W at 1.94 µm optical wavelength had been used for the *ex vivo* experiment on human prostatic tissue. The rate of tissue vaporization and zone of thermal coagulation were assessed.

Results: The in-house made (CSIR-CGCRI, Kolkata, India) CW TFL used at power of 60 W at 1.94 µm was capable of providing tissue vaporization rate of 0.13–0.45 g/min with a thermal coagulation zone of 100 µm.

Conclusions: In our study, the TFL was efficient in vaporization, vaporesection, and coagulation of the prostatic tissue under controlled circumstances. Compared to the existing laser systems, the TFL could be a new alternative in Endourology.

Keywords: Benign hyperplasia of prostate, *ex vivo* vaporization of prostate, thulium fiber laser

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INTRODUCTION

With increase of aging population, the prevalence of benign prostate hyperplasia (BPH) has increased worldwide. Open prostatectomy and transurethral resection of the prostate (TURP) are the standard techniques of surgical management for BPH.[1] Open prostatectomy is associated with significant morbidity on account of the invasiveness of the procedure. As per the European Association of Urology guidelines, TURP has been recommended as the gold standard minimally invasive treatment for prostatomegaly in prostates 80 g or less in

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size. However, for the treatment of larger prostate glands, newer minimally invasive endourological thermal therapy technologies have evolved such as lasers, therapeutic ultrasound, and microwave thermal therapy. These thermal modalities impart their effect through ablative and coagulative mechanisms of action.[2] Coagulative techniques such as microwave therapy and therapeutic ultrasound uses energy to heat up the prostatic tissues to temperatures above 50°C which results in thermal denaturation. This leads to coagulative necrosis and sloughing of tissues in the post operative period. Whereas ablative techniques such as Holmium: Yttrium-aluminum-garnet (Ho: YAG) and Potassium titanyl phosphate (KTP) laser help in direct removal of tissues through incision and vaporization by elevating the tissue temperatures above 100°C.[2,3]

Considering the risks of bleeding in patients with coagulopathy or on anticoagulant therapies, development of transurethral resection syndrome during prolonged surgery and possible other complications during TURP, laser technology including neodymium, thulium, Ho: YAG, KTP, and diode laser have been explored in recent years.[2-4]

In laser-based surgery, the focused beam of light generates precise and intense heat to vaporize excess prostate tissue or to incise the excess tissue into small pieces. The use of laser vaporization and enucleation depends on the size of prostate, physical condition of the patient, type of available equipment, and expertise. Laser surgery can offer several advantages over TURP and open prostatectomy such as low risk of bleeding, shorter hospital stay, quicker recovery, and earlier trial without a catheter.[5]

Ho: YAG (λ=2.12 μm) laser is a gold standard clinical tool in urology on account of its diverse nature of clinical applications.[4] Thulium: YAG (Tm: YAG; λ=2.013 μm) laser have presently become a promising alternative laser for the surgical management of BPH.[5] The Tm: YAG laser uses continuous wave (CW) energy to achieve tissue vaporization while Ho: YAG uses pulsed wave energy that mainly acts by tearing of soft tissue and have limited vaporizing effect. High powered Tm: YAG laser of up to 200 W CW is now in clinical use. The CW mode of laser allows simultaneous operation of vaporization, vaporesection, and vapoenucleation of the prostate tissue without much bleeding.[6]

The operating wavelength of Tm: YAG laser is 2.013 μm which does not match with the cellular water absorption peak in tissue (1.94 μm). Thulium fiber laser (TFL) on the other hand can operate at a wide range of wavelength between 1.75 and 2.22 μm which includes the desired point where the water absorption peak is located. The higher water absorption gives better efficiency in tissue vaporization and ablation with less penetration of the surrounding areas leading to less peripheral thermal damage.[6,7] In fact TFL is capable of reducing thermal damage of the surrounding tissues by a factor of four compared to a 2.12 μm holmium laser.[6] The lasing medium of a TFL is located within the thulium doped silica optical fiber which is pumped by a diode laser. This provides higher wall-plug efficiency (6%) compared to holmium laser and KTP laser (1%–2%).[2,6] The diode pumped TFL can operate in CW mode which is suitable for hemostasis and coagulation of tissue and also work in pulsed mode effective for precision cutting of tissues. This makes TFL a more versatile option for therapeutic usage. Tm: YAG laser consists of YAG crystals, requires a 220 Volt electrical outlet for high powered operation, water cooling system and a combination of mirror based system, making it bulky and difficult to transport. TFL on the other hand is a compact, table-top device that can be operated with any standard 110V electrical outlet and with better maintenance free operation.[6] Hence, TFL can be an attractive alternative laser for urological surgeries. In terms of laser characteristics, TFL is technologically superior over YAG lasers for surgical use.

This paper depicts the work done in initial validation of an in-house designed TFL in *ex vivo* vaporization and vaporesection of human prostatic tissue. We also tried to study the efficiency of the TFL and its effect on the surrounding tissue in terms of coagulation and energy dissipation. The ablation rate and thermal coagulation zone of the in-house (CSIR-CGCRI) designed TFL was compared to 200W Tm: YAG laser (Quanta System, Cyber TM).

METHODS

An in-house (CSIR-CGCRI, Kolkata, India) designed TFL having maximum CW power level of 70 W at 1.94 μm was used for this *ex vivo* experiment [Figure 1]. The laser can also be operated in a long-pulse mode through the modulation of the pump laser diodes. The laser beam was coupled with a low-OH silica optical fiber of 550 μm core diameter. The laser specifications are given in Table 1.

Prostatic tissue samples were collected from 10 different patients after TURP or simple prostatectomy and were studied *ex vivo*. These tissues were collected after completion of surgery at a tertiary care centre in Eastern India under ethical clearance (IPGMEandR/RAC/102 dated December 26, 2019). All samples were

kept refrigerated until use. The samples were kept in normal saline to hydrate during experiments, but not completely immersed. Both the Tm: YAG laser and the TFL had been exposed to the samples in CW mode with different power levels. There was a continuous flow of normal saline to keep the tissue sample surface hydrated during vaporization. The laser beam was then focused into the 550 μm laser fiber and delivered to the prostatic tissue samples. The hand held holder for laser fiber had been moved in such a way so that the tissue surface was processed uniformly. The temperature at the laser delivery fiber tip was measured through Thermal Camera (Thermal Camera E53 FLIR by Teledyne, USA). The rate of tissue vaporization (g/min) had been estimated through precise weight measurement of the wet tissue by a micro weighing scale (HPB 201 High Precision Balance by Wensar, India) before and after laser exposure and was divided by the laser exposure time. The laser incised tissue specimens were preserved in 10% formalin solution and were sent for histopathological assessment. The thermal coagulation zone and the ability to achieve haemostasis by the laser were evaluated after histopathological analysis of the zone of charring and zone of coagulation of the TFL incised tissue specimens.

RESULTS

A total of three human prostate lumps (mean weight = 4.19 ± 0.84 gm) have been vaporized using TFL [Table 2]. The estimated average rate of vaporization of tissue is 0.13 ± 0.04 g/min under TFL CW power of 60 W. The temperature of the delivery fiber tip was within 40°.

A set of post-TURP prostate chips having mean mass of 0.156 ± 0.02 g have been vaporized completely at an average rate of vaporization of 0.44 ± 0.07 g/min under TFL CW power of 60 W. The temperature of the delivery fiber tip was also within 40°C [Table 3].

In terms of ability to incise the prostatic tissue, the TFL was capable of cutting human prostate tissue of 2.5 cm ± 0.5 cm length and depth of 1 cm ± 0.2 cm within 4 min of exposure to 60 W CW TFL. The incised prostate tissue is shown in Figure 2. The static exposure of 0.5 s can create carter of 1 mm depth, 1 s create depth of 2.5 mm and 2 s exposure create depth of 4 mm. The hematoxylin and eosin stained tissue sections shown in Figure 3 demonstrates a thin layer (40 μm) of carbonization followed by a 100 μm layer of cellular vacuolisation and

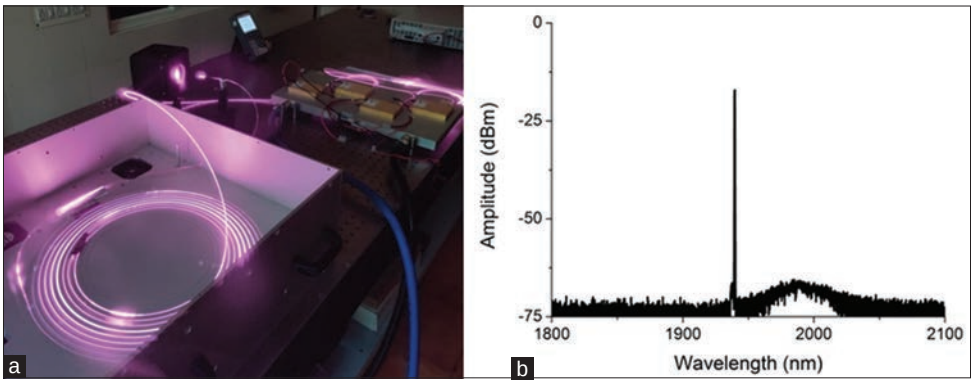

Figure 1: (a) In house TFL system, (b) TFL spectrum having centre Wavelength at 1.94 μm. TFL: Thulium fiber laser

Table 1: In-house designed thulium fiber laser specification versus Holmium: Yttrium aluminum garnet and Thulium: Yttrium-aluminum-garnet laser

	In-house thulium fiber laser	Ho: YAG	Tm: YAG (quanta system, cyber Tm)
Operating wavelength (μm)	1.94	2.12	2.013
Mode of operation	CW/pulsed	Long pulsed	CW
Frequency (Hz)	10–1000	5–80	-
Maximum output power (W)	70	120	200
Beam quality	Single mode	Multi-mode	Multi-mode
Laser delivery fiber core diameter (μm) min	150	200	200

Ho: YAG: Holmium: Yttrium aluminum garnet, Tm: YAG: Thulium: Yttrium-aluminum-garnet, CW: Continuous wave, TM: Thulium

Table 2: Thulium fiber laser vaporization of large sections of human prostate

Sample ID	Time (min)	Initial weight (g)	Postvaporization weight (g)	Vaporization rate (g/min)	Local heat at fiber tip (°C)
Sample-A	20	3.27	0.7	0.13	34
Sample-B	20	4.92	2.08	0.14	38
Sample-C	20	4.40	1.75	0.13	36

Table 3: Thulium fiber laser vaporization of human prostate chips

Sample ID	Initial weight (g)	Complete vaporization time (s)	Vaporization rate (g/min)	Local heat at fiber tip (°C)
Sample-D	0.103	17	0.36	35
Sample-E	0.123	20	0.37	40
Sample-F	0.121	17	0.43	36
Sample-G	0.147	16	0.55	34
Sample-H	0.151	21	0.43	38
Sample-I	0.211	27	0.47	40
Sample-J	0.236	27	0.52	40

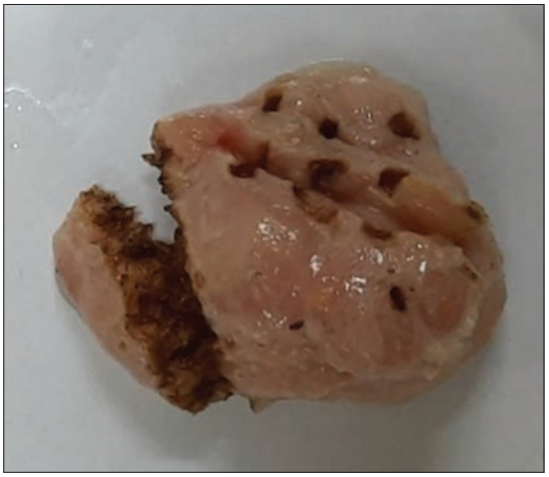

Figure 2: Human prostate tissue incision by 60 W TFL. TFL: Thulium fiber laser

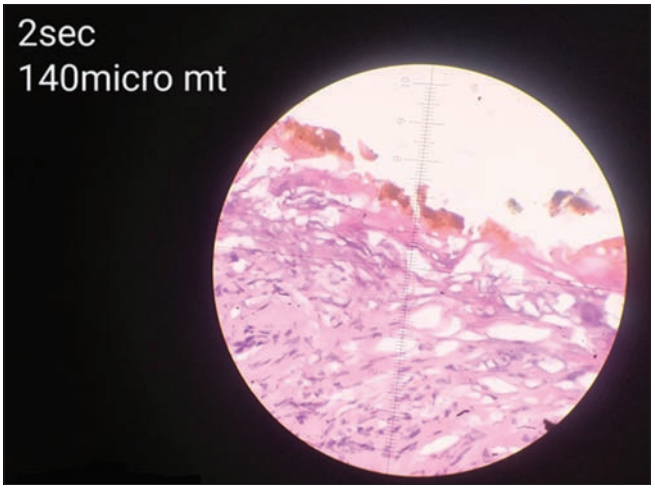

Figure 3: Histopathological assessment of the prostatic tissue specimen post TFL use. A 40 µm zone of carbonisation followed by a 100 µm cellular vacuolisation and thermal coagulation zone is seen here. TFL: Thulium fiber laser

thermal coagulation zone. After using Tm: YAG laser in a similar fashion, the histopathological assessment of prostate tissue sections showed a 200 µm zone of cellular vacuolization and thermal coagulation. The charring effects of Tm: YAG laser were excess compared to the TFL. This thermal coagulation zone gives us an impression that the TFL would not only be able to provide fast incision and vaporization rates but also be able to provide haemostasis in prostatic tissue with less thermal damage of surrounding tissues. Thus TFL would preserve the histopathological hallmark of the disease.

DISCUSSION

The purpose of this study was to test an in house designed (CSIR-CGCRI, Kolkata, India) TFL for its potential use in prostatic tissue ablation techniques in endourological procedures. In our study, the TFL was efficient in vaporization, vaporesection, and coagulation of the prostatic tissue under controlled circumstances. However, before prescribing this system, the results need to be compared to the existing laser systems available to determine its advantages and disadvantages.

In this study, the diode pumped CW TFL working at a power of 60 W at 1.94 µm optical wavelength was capable of providing tissue vaporization rate of 0.13–0.45 g/min. It was lower than that for 80W KTP and 100W Ho: YAG laser which was capable of achieving tissue vaporization rate of 1–2 g/min.[8,9] The lower and variable ablation rate seen in this experiment may be due to the lower power use as well as use of tissues of different sizes and bulk. It is assumed that the ablation rate is linearly dependent on the laser power. Although TFL s with up to 150 W output are commercially available for industrial purposes, these are expensive and were not available during this study.[6] Therefore, increasing the power delivered to the tissues from 60W to up to 150W would achieve an ablation rate >1.2 g/min.[10,11] The rate of vaporization is guided by the selected distance from the laser fiber to the tissue surface, sweep speed and sweep angle. The proper vaporization occurs when the laser beam creates thermal energy above the boiling (or vaporizing) point for the tissue. Hence more power would be proportional to faster ablation rates but at the risk of damage to the surrounding structures.[12,13]

On the other hand lesser laser power creates more carbonization during vaporization. The incision performance is better for lower power with less damage to the peripheral tissue. As with Holmium and KTP

lasers which were initially used at low power levels and then gradually progressed to higher power to be used in urosurgical practice, TFL is being studied in similar fashion for its potential use in prostate surgery.[6,10]

In this study the thermal coagulation zone around the area of prostatic tissue incision was 100 μm which was half as less as compared to the 100 W Tm: YAG laser (Quanta System, Cyber TM) and one fourth to that of other *ex vivo* 100 W Ho: YAG laserstudies.[6,11] Other contemporary *ex vivo* experiments of 40W TFL on animal prostate tissues showed a considerably wider (400–600 μm) of thermal damage zone. This wider thermal damage zone seen in this study may be due to the use of longer pulse (10 m s) and higher pulse-repetition rates (20–50 Hz).[6] In our study we have used the TFL in a CW mode using 60 W maximum output of power, which might have been the factor behind lesser thermal damage zone.

To avoid injury to the surrounding structures albeit with efficient coagulation, high-powered TFL use with short-pulse duration may be helpful. High-powered TFL with short-pulse frequency can be an alternative option to Holmium laser in lithotripsy. Further studies need to be done in this field before TFL can be prescribed as an efficient alternative to existing laser systems.

CONCLUSIONS

This initial *ex vivo* study is to demonstrate the efficacy of an in-house developed TFL in prostatic tissue vaporization and incision. This is for better understanding of the TFL technology and possible problems and complications during its use with respect to the available surgical options in tissue application. The work is progressing for the development of high powered TFL to expose the prostatic tissue to more power to study the vaporization and incision properties. The wide range of TFL use in CW and pulsed mode will make the same system suitable for both lithotripsy and tissue surgery. The compact TFL design makes it easy to move to different locations and makes the system more economic for applications in different modes of treatment in urology.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

The islanded nasolabial flap for tongue reconstruction – Experience in our institute

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Abstract

Background: Oral cancer ranks in the top three of all cancers in India, which accounts for over thirty per cent of all cancers reported in the country. Tongue cancers make a significant percentage among the oral cancer burden. Unfortunately, patients rarely present to the surgeon with a tongue cancer lesion small enough for a primary closure. Hence we frequently need some type of flap for reconstruction of the tongue defect following ablative surgery. In defects that are not small enough for a primary closure as well as not big enough for a more bulky flap like the PMMC or the free ALT flap, the islanded nasolabial flap is of great use to the surgeon for tongue reconstruction and should be part of the reconstructive armamentarium of every oral cancer surgeon.

Aims and Objectives: To assess the difference in post-operative speech results between patients having flap reconstruction versus patients having primary closure, and to assess the complications of islanded nasolabial flap reconstruction.

Materials and Methods: Retrospective study of 6 months with 11 patients having islanded nasolabial flap reconstruction and 18 patients having primary reconstruction.

Results: Post-operative speech results of patients with flap reconstruction were as good as those having primary closure.

Conclusions: Islanded nasolabial flap may be a good option for reconstruction of carefully selected tongue defects.

Keywords: Islanded nasolabial flap, reconstruction, tongue cancer

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INTRODUCTION

Microvascular-free flaps are the preferred method of tongue reconstruction at present. However, local flaps have their own utility in carefully selected cases. Random nasolabial flaps have been used in the past for the reconstruction of small oral cavity defects. A modified nasolabial flap, islanded on the facial vessels, is a further improvement on the random flaps of the past. It has its own advantages such as long vascular pedicle, a large arc of rotation, and good soft tissue bulk. In this article, we share our institutional experience in using the islanded nasolabial flap (NLF) for reconstruction after ablative surgeries for tongue cancer.

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MATERIALS AND METHODS

This was a retrospective study conducted in the Institute of Otorhinolaryngology and Head and Neck Surgery, IPGME&R, Kolkata. Records of patients in the past 6 months (January 2022 through June 2022) were reviewed and 11 patients were found to have had islanded NLF reconstruction for their tongue defects. These 11 patients were included in the study. Data were analyzed regarding age and sex of the patients, clinical T-stage, preoperative speech intelligibility score (SIS), 3 months postoperative SIS, and reported complications. In addition, the mean postoperative SIS of the patients was compared to that of patients undergoing primary closure of their tongue defects in the same study period (n = 18) to look for any statistically significant difference between the two groups.

Surgical technique

Decision to do an islanded NLF has to be taken in advance, as during the neck dissection, the facial artery and veins need to be preserved (they are generally sacrificed otherwise). Facial skin laxity is another factor that needs to be assessed before deciding on this flap.

The flap is designed fusiform in shape. The flap dimensions generally mimic the dimensions of the tongue defect. It is prudent to keep the length: breadth ratio as 2.5–3:1 to prevent distal necrosis. Furthermore, width >3 cm is not recommended as the donor area will be difficult to close primarily otherwise.

The superior limit of the flap is about 1–2 cm below the medial canthus to prevent ectropion. The lower limit is at or just below the anterior commissure. The medial limit is about 2–4 mm lateral to the nasolabial fold; the groove is avoided to prevent poor cosmetic outcomes [Figure 1].

After injecting the planned incision line with local anesthetics and vasoconstrictor, the flap harvesting is commenced in a superior-to-inferior direction. The skin and subcutaneous fat are incised until the buccinator muscle is identified. The facial vein is identified and clipped at the superior aspect of the flap. Dissection is continued inferiorly in a plane between the facial vein above and the buccinator muscle below. The medial incision is then completed to identify the facial artery. All the branches of the artery medial to the flap, including the labial arteries, are clipped. Dissection is continued in a plane below the artery, and the vessel is clipped high up in the flap. The lateral incision is committed at this point, and the flap is dissected from superior-to-inferior and medial to lateral in a plane below the facial vessels.

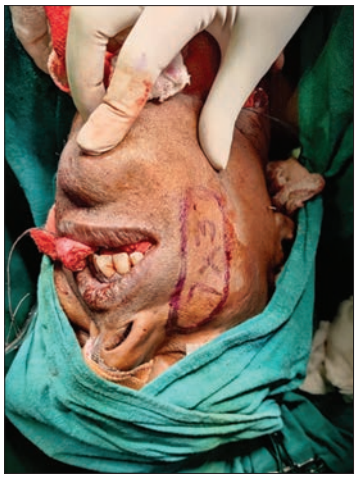

Figure 1: Dimensions of the flap

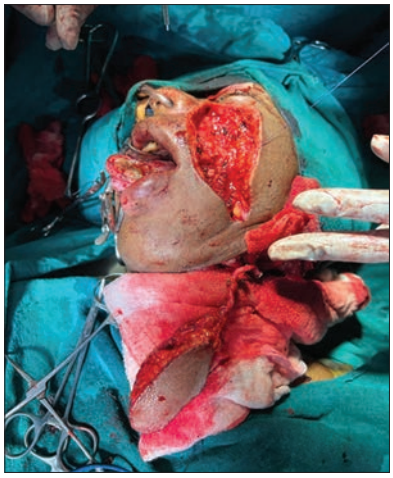

Figure 2: Flap islanded on the facial vessels

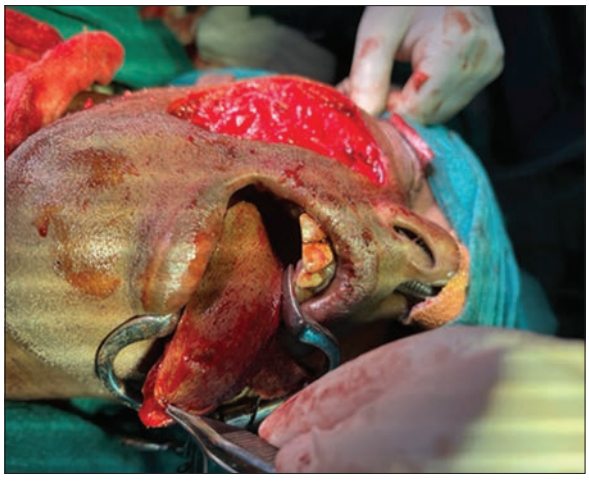

Figure 3: Inset of the flap

The flap is then completely islanded on the facial vessels [Figure 2]. The flap is delivered into the oral cavity or oropharynx medial to the mandible either through the resected floor or through the mylohyoid by splitting the muscle fibers. Inside the oral cavity, the flap

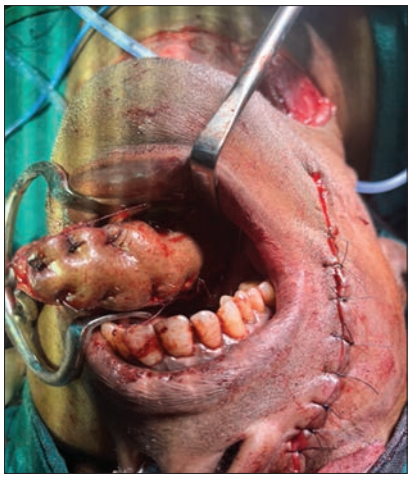

Figure 4: Donor site closure

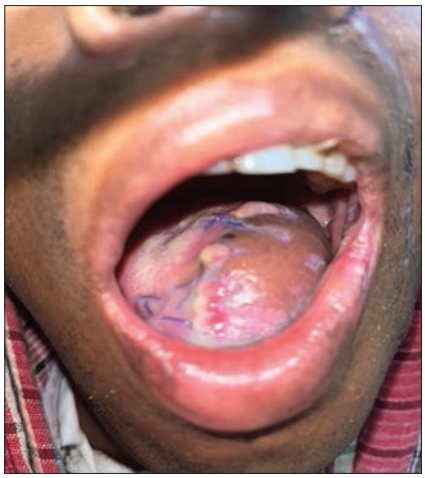

Figure 5: Final result

is positioned such that the distal part of the flap (i.e., superior) goes anteriorly [Figure 3]. This is done as the distal tip, being farthest from the facial artery, is more vulnerable to ischemia, and if it occurs, it can be easily accessed intraoral for primary closure. The donor site is then closed primarily in a tension-free manner [Figure 4]. The postoperative result is shown in Figure 5.

RESULTS

Of the 11 patients, 9 (81.81%) were male and 2 (18.19%) were female. The mean age of the patients was 46.54 ± 9.33 years. Seven (63.64%) patients were in clinical T-stage 2, whereas 4 (36.36%) patients were in stage 3 [Table 1].

Records of the preoperative SIS of the patients were accessed, and it was compared to the postoperative SIS of the same patients using paired *t*-test. There was a statistically significant difference in postoperative versus preoperative SIS of the patients; $t(10) = 7.4550$, $P < 0.0001$, which is expected in any ablative surgery on the tongue [Table 2].

In addition, the postoperative SIS of this group was compared to that of a group of patients who had undergone ablative surgeries of the tongue and reconstructed with primary closure of the defect, using independent samples *t*-test. There was no statistically significant difference between the two groups; $t(27) = 1.3643$, $P = 0.1837$.

Complications such as marginal mandibular nerve palsy, flap loss, and orocutaneous fistula were encountered, and are shown in Table 3.

Table 1: Patient characteristics

	n (%)
Sex	
Male	9 (81.81)
Female	2 (18.19)
T stage	
T2	7 (63.64)
T3	4 (36.36)

Table 2: Comparing preoperative versus postoperative speech intelligibility scores

Patient serial number	Preoperative SIS	Postoperative SIS
1	5	4
2	5	4
3	6	3
4	5	3
5	5	4
6	6	5
7	4	2
8	6	5
9	4	3
10	5	3
11	6	4

SIS: Speech intelligibility score

Table 3: Complications

Complications	*n* (%)
Marginal mandibular nerve palsy	4 (36)
Flap loss	2 (18)
Orocutaneous fistula	1 (9)
Nil	6 (54)

DISCUSSION

Tongue cancer is one of the most aggressive cancers of the oral cavity in India. One of the challenges in its management is proper reconstruction following resection because of the various functional aspects.[1] Reconstruction of defects in tongue cancer is essential for providing lining and bulk needed for speech articulation as well for swallowing.[2] Various reconstructive options for tongue defects are primary closure, locoregional flaps, and distant microvascular flaps.

Of these, free flaps are the choice of reconstruction, especially for larger defects.

NLF is found to be a very good choice for smaller defects as compared to flaps such as pectoralis major musculocutaneous pedicle flap, free forearm radial flap, or anterolateral thigh flap as the latter need prolonged surgical and anesthesia time, microvascular expertise, and the bulk of the flaps often cause mobility restriction, especially in females.[3] The donor site morbidity and prolonged healing process due to restricted mobility causing contracture also raise problems. NLF is a locally available flap which combines the pliability of the skin with the bulk required for the reconstruction of the tongue thus helping to preserve the function of the tongue and thereby to improve the quality of life of the patient.[4]

However, this type of reconstruction is not particularly suitable when teeth are present in the area to be reconstructed, and biting on the pedicle may even damage the skin.[5]

It is here that the importance of island NLF comes up. The NLF can be done either islanded or keeping the skin pedicle intact. Island NLF is a modification of conventional NLF by islanding it over the facial artery and vein as pedicle and dissecting them until the origin. This gives a long length to the pedicle, making it reach anywhere in the oral cavity.[6] This flap is then taken inside the oral cavity by tunneling through the floor of the mouth, making it very identical to free flap. The major advantage of this approach is its applicability in dentulous patients. The other advantages of this type of flap include less surgery duration, no need for microvascular setup, good tongue mobility, adequate bulk, cost-effectiveness, onco safe approach, and minimal hair growth.[1]

CONCLUSION

Thus islanded nasolabial flap should be considered a locoregional flap of choice and an alternative to free flap for tongue reconstruction.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Are there any abnormalities in lipid profile of post-COVID patients: A case–control study?

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Abstract

Background: It is well known that viral infections alter lipid metabolism in a way that promotes viral proliferation. Numerous studies have shown that people with coronavirus disease-2019 (COVID-19) have a significant impact on patients' lipid profiles. To evaluate whether any lipid profile aberrations are still present in those who had COVID-19 infection more than 6 months ago, our purpose is to compare the lipid abnormalities in post-COVID patients to those in non-COVID patients.

Methods: We have taken blood samples from 108 post-COVID-19 patients (cases) and 108 nonsmokers who are age- and sex-matched as controls. Using the blood sample, a lipid profile test was conducted to measure total cholesterol, high-density lipoprotein, low-density lipoprotein (LDL), very LDL, and triglycerides.

Results: Data analysis demonstrates that all of the results are statistically significant, with the exception of the LDL cholesterol (LDL-C) value, which is statistically nonsignificant.

Conclusion: With the exception of the LDL-C value in post-COVID-19 individuals, we were able to identify noticeable alterations in lipid profiles. It is a fact that most investigations have found abnormalities in lipid profiles during the disease's acute phase. Future studies must examine whether the lipid profiles of individuals after COVID-19 underwent any discernible changes with a larger sample size and a longer study period.

Keywords: Case–control, lipid profile, post-COVID

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INTRODUCTION

Lipids have a variety of metabolic roles, including those of structural elements, energy sources, signaling mediators, and mediators in infections, particularly viral infections. Lipids are necessary for a number of immune and macrophage-regulatory processes, and studies have shown that inflammation and lung infections are related to lipid metabolism.[1,2] In addition, they are necessary for viruses to get through the host cell membrane. In addition, viral infections are known to change lipid metabolism in a way that facilitates virus replication.

Since lipids not only make up the majority of the membrane structure but also play crucial functions as intercellular signal transduction and energy sources, viruses exploit and change both lipid signaling and metabolism to aid in their reproduction.[3]

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Numerous investigations have demonstrated that individuals with coronavirus disease-2019 (COVID-19) have intensely different lipid profiles, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). TC builds up in the cell membrane, which enables membrane fusion and viral entrance into the host cells.[4,5]

COVID-19 is caused by the coronavirus that manifests severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the respiratory system is frequently affected, 20%–30% of very sick people and some asymptomatic people have cardiovascular involvement during the disease and suffer some consequences.[6]

Significant lipid profile abnormalities, particularly those involving LDL-C levels, are associated with severe cardiac issues. The majority of the research revealed that changes in lipid profiles happen during the acute phase of COVID-19 infection. However, there is little research on how the lipid profile changes after a COVID-19 infection. Our objective is to compare the lipid abnormalities in post-COVID patients to those in non-COVID patients to determine whether any lipid profile alterations are still present in individuals who had COVID-19 infection more than 6 months past.

METHODS

Setting of the study

The study was carried out in West Bengal, India, in the department of biochemistry at a tertiary care hospital, a national research institute.

Type of the study

It is a case–control study including the lipid profile of post-COVID patients (more than 6 months after the disease attack) with age- and sex-matched nonsmoker controls.

Duration of the study

The study was conducted from July 1, 2022, to August 11, 2022.

Data collection

Blood samples from the participants were taken, and the samples were used to do a test on the lipid profile (TC, HDL, LDL, very LDL [VLDL], and triglycerides [TGs]). The information was gathered and organized based on patients with COVID-19 and control patients. Data from a sample of patients who developed COVID-19 was used as the experiment's "cases," whereas data from patients who did not develop COVID-19 was used as the experiment's "control data." We used 108 post-COVID-19 patients as cases and another 108 people (matched for age, sex, and abstinence from smoking) as controls. Each participant freely provided their informed consent. Patients who refused to give their consent were excluded from the study. Patients using lipid-lowering medicines for lipid abnormalities were also not included in the research.

Data analysis

The information was set up in a Microsoft Excel sheet. In accordance with control and cases, lipid profiles (TC, HDL-C, LDL-C, VLDL-C, and TG) were listed. The mean value of the data was computed using a conventional statistical procedure. Standard statistical techniques were used to calculate the variables' *P* values.

RESULTS

In our study, 108 individuals served as the control group, whereas 108 post-COVID-19 patients served as the cases. They belonged to the age range of 25–84 years. They were divided into six groups. They included five men and six women in the control group and six men and eight women as cases in the age range of 25–34 years. In the age range of 35–44 years, 17 men and nine women made up the case group, whereas 16 men and 15 women made up the control group. The control group included 10 men and 14 women aged 45–54 years, whereas the cases included 12 men and 12 women. There were 13 men and 12 women in the control group, and nine men and 10 women in the age range of 55–64 years who were cases. The case group had eight men and nine women between the ages of 65 and 74 years, whereas the control group included six men and six women. Five males and three females in the 75–84-year-old age range made up the case group, whereas two males and three females made up the control group [Table 1].

The mean TC level in the control group is 190.136 mg/dl, whereas HDL cholesterol is 48.489 mg/dl, LDL cholesterol is 109.994 mg/dl, VLDL cholesterol is 31.274 mg/dl, and TG is 153.994 mg/dl. The mean TC level in post-COVID cases is 188.677 mg/dl, relative to 48.120 mg/dl for HDL,

Table 1: Age group-wise distribution of the patients

Age group	Cases		Control	
	Male	Female	Male	Female
25-34	6	8	5	6
35-44	17	9	16	15
45-54	12	12	10	14
55-64	9	10	13	12
65-74	8	9	6	6
75-84	5	3	2	3
Total	57	51	52	56

111.726 mg/dl for LDL, 29.601 mg/dl for VLDL, and 148.051 mg/dl for TG [Figure 1]. All of the numbers are statistically significant, according to the data's statistical analysis, with the exception of the LDL cholesterol value, which is statistically nonsignificant [Table 2].

DISCUSSION

In this study, we examined the lipid profiles of 108 recovered COVID-19 patients and a control group of 108 patients more than 6 months after discharge. In comparison to the control group of participants, our data show that levels of TC, HDL cholesterol, VLDL cholesterol, and triglycerides were mildly altered; however, statistical analysis of the data shows that all of the values are statistically significant, with the exception of the LDL cholesterol value, which is statistically nonsignificant. The severity of the symptoms is correlated with the decline in lipid levels in acute cases of COVID-19 patients. Therefore, decreasing blood cholesterol levels may signal severe peripheral tissue cholesterol loading and increased SARS-CoV-2 infectivity. According to Cao *et al*., cholesterol may promote an acceleration of SARS-CoV-2-induced endothelium damage.[7] According to Sorokin, people with COVID-19 who had lower HDL-C levels had lower antioxidant and anti-inflammatory effects of inflammatory pulmonary disease and HDL-C.[8]

Low HDL-C and high TG before infection and upon admission were major indicators of disease severity, according to a cross-sectional examination of 1411 hospitalized COVID-19 patients.[9] While TC and LDL-C were lower in all COVID-19 patients, and LDL-C decreased as the condition worsened, another sizable investigation revealed that HDL-C was only abnormally lower in severe instances.[10] Another research on 228 instances of COVID-19 in China found that LDL-C, HDL-C, and TC were lower in these patients than in healthy controls and that lower HDL-C upon admission was a poor predictive indicator for poor disease outcomes.[11]

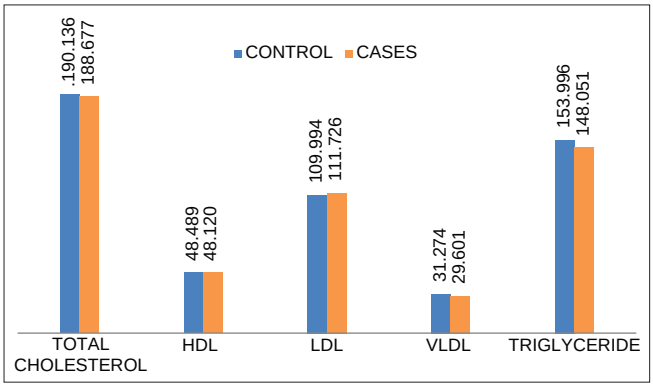

Figure 1: Column diagram depicting the levels of lipid components (average values)

HDL-C and Apo-A1 are negatively connected to disease severity indicators like mortality rate and inflammatory markers like C-reactive protein (CRP) and interleukin-6, according to two prospective studies to analyze lipid changes in COVID-19.[12] In addition, they observed that their severe patients had considerably greater TG levels compared to their milder patients, as well as lower TC and LDL-C values.[13] In several investigations, LDL and HDL were shown to be negatively correlated with CRP, a measure of the degree of inflammation.[11,14]

In a retrospective analysis of the lipid profiles of 248 COVID-19 patients, they discovered lower levels of TC and LDL-C. The length of the patients' hospital stay was inversely linked with these measurements.[14]

Low levels of TC and LDL-C may be able to predict more severe involvement, according to another retrospective study conducted on 102 patients in Mexico. They also reported having elevated TG and VLDL-C values.[15] According to Saudi Arabian research of 80 COVID-19 patients, the patients' lipid profiles have changed, with lower levels of TC (both HDL-C and LDL-C) and higher levels of TG.[16]

Most investigations have found that the lipid profiles of COVID-19 patients have changed, with TG levels rising and cholesterol and apolipoprotein levels falling. Another research found no link between the recovery of LDL-C or HDL-C levels.[17]

Lipidomic investigations have uncovered that coronavirus altogether adjusts the lipid composition of infected cells.[18] Viruses utilize and adjust both lipid signaling and digestion system to advantage their replication as

Table 2: The levels of lipid components (average values) and *P* values

	Total cholesterol (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)	TG (mg/dl)
Control (average)	190.136±9.62	48.489±4.29	109.994±6.67	31.274±3.48	153.996±7.82
Case (average)	188.677±9.38	48.120±4.18	111.726±7.16	29.601±3.85	148.051±6.93
Control (range)	114.3–286.69	37.8–58.2	31.83–194.87	16.27–89.66	28.51–448.33
Case (range)	116.41–282.29	34.28–57.19	65.87–187.64	16.26–270.12	81.3–466.8
P	0.00001	0.01324	0.08113	0.0184	0.0001
Statistical significance	Statistically significant	Statistically significant	Statistically nonsignificant	Statistically significant	Statistically significant

HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, VLDL-C: Very-LDL-C

lipids constitute not as it were the most structure of membranes but moreover play vital parts as intercellular signaling specialists and vitality sources.[19] Replication of encompassed infections like SARS-CoV-2 which enter the cells through endocytosis and utilize intracellular organelles to deliver their distinctive parts requires lipid resources.[20] Thus, contamination with SARS-COV-2 influences the lipid digestion system and profile and sheds light on the relationship between lipid profile and provocative forms amid COVID-19.

However, in the current investigation, we did not show any appreciable changes in the LDL-C level of post-COVID-19 patients, although most of the studies have found low LDL-C levels in cases of acute COVID-19 patients.[10,11,13-17] Since the people have been symptom-free for a while now, it can be concluded that their viremia is either nonexistent or very low. As a result, the altered LDL-C level may have returned to normal homeostasis since the virus is not using the usual metabolic pathway of lipid metabolism for its replication. According to the patient's statement, it was also noted that they were conscious of their daily calorie consumption and engaged in some type of physical activity as indicated by primary care physicians monitoring post-COVID-19 patients on a regular basis.

Study limitations

The study was conducted over a relatively brief period of time, and the sample size was also rather small.

Future directions of the study

Future directions of this study should involve a larger sample size and a longer study period to see whether patients who had COVID-19 experienced any significant alterations in their lipid profiles.

CONCLUSION

We took the opportunity to investigate any alterations in lipid profiles of post-COVID-19 patients because the majority of researcher has found abnormalities in lipid profiles in the acute phase of the illness. Aside from LDL-C value in post-COVID-19 participants, we were also able to detect substantial changes in lipid profiles in this investigation. Future research must determine whether, with a bigger sample size and a longer study period, the lipid profiles of people after COVID-19 underwent any noticeable alterations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Rhino-cerebral mucormycosis storm during COVID-19 pandemic: A retrospective study at urban tertiary care center

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Abstract

Introduction: The imminent threat has emerged in the form of COVID-19-associated opportunistic infections in India. Mucormycosis has been increasingly described in patients with severe COVID-19 disease. We attempted to study the epidemiological factors, clinical presentation, and outcome in such patients which have not been well described.

Materials and Methods: A total of 47 patients diagnosed with mucormycosis infection in tissue sections of patients with a history of COVID-19 disease were included in the study. A detailed clinical history including radiological and microbiological findings was retrieved from the case sheets. Histopathology slides were reviewed and correlated with clinical findings.

Results: The males were commonly affected than females. The most common age group for females was slightly more than males. Out of 47 patients of mucormycosis, 37 (78.72%) have associated diseases. The 29 were known patients of diabetes mellitus, of which 16 patients had also associated hypertension. Thirty-nine patients received steroids during the hospital stay. Treatment with steroids and hyperglycemia were the most common risk factor for mucormycosis in post-COVID-19 disease.

Discussion: Apart from severe COVID-19 disease, treatment with steroids, and hyperglycemia, other possible factors for mucormycosis include immune dysregulation and hyperferritinemia. Early diagnosis and treatment are the keys for the reduction of morbidity and mortality. Early diagnosis of mucormycosis requires expertise and interdisciplinary co-ordination. Craniofacial pain in patients with a history of severe COVID-19 disease, a diagnosis of mucormycosis must be suspected.

Conclusion: Early diagnosis of mucormycosis.

Keywords: COVID-19, hyperglycemia, mucormycosis, severe, severe acute respiratory syndrome

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INTRODUCTION

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected India substantially and has claimed thousands of lives in the country. It has wide range of disease pattern ranging from

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mild-to life-threatening pneumonia.[1] Another imminent threat has emerged in the form of COVID-19-associated opportunistic infections. These patients are prone to develop wide range of bacterial and fungal co-infections which add significant morbidity and mortality to disease.[1-3] Globally, and in India, there is substantial increase in mucormycosis cases after severe COVID-19 infection.[2-4]

Many risk factors for mucormycosis infection have been implicated such as COVID-19, diabetes mellitus, chronic lung diseases, immunocompromised status due to corticosteroid therapy for immunosuppression, and long-term stays in the intensive care unit. Due to steady rise in the number of mucormycosis cases and deaths related to it, many states in India were forced to declare it as an epidemic and a notifiable disease to the national health authorities.[5]

We came across with very few large series studies of COVID-19-associated mucormycosis in the Western and Indian literature.[6,7] The purpose of this study is to identify important risk factors for mucormycosis infection in post-COVID-19 infection to study the clinical presentation of the disease. We report 47 cases of mucormycosis diagnosed on histopathological examination at tertiary care center in the western part of India.

MATERIALS AND METHODS

A single center retrospective descriptive study was carried out in urban tertiary care center in the western part of India between April 15, 2020 and June 30, 2021.

Informed written consent was obtained from patients participating in the study. All procedures performed in the study were conducted in accordance with the ethics standards. In view of retrospective study, ethical clearance for the study was waived by the Institutional Ethical Committee. Inclusion criteria: Post-COVID-19 patients diagnosed with mucormycosis infection in tissue sections were included in study. Exclusion criteria: Patients already diagnosed with mucormycosis outside centers were excluded from the study.

A detailed clinical history, including radiological and microbiological findings, was noted from the case sheets. Biopsy or surgical tissues of these patients received for histopathological examination were looked for pathology. Specimens received for histopathological examination were fixed in 10% formal saline. Adequate sections were taken and processed with paraffin. The 3–5 μm thick sections were cut and stained with routine Hematoxylin and Eosin (H and E). Fungal stains such as periodic acid Schiff (PAS) and grocott methanamine silver (GMS) were done whereever required. Final diagnosis was based on the histopathological features and was correlated with clinical findings. Statistical analysis: Results were analyzed correlated and reported in the numerical and tabulated form.

RESULTS

The 47 patients were diagnosed of mucormycosis in biopsy or surgical specimens by identifying fungal hyphae of mucormycetes. H and E sections showed broad, thin-walled pleomorphic nonseptate hyphae. In five cases, thick-walled chlamydoconidia were seen [Figure 1a]. An inflammatory infiltrate of polymorphonuclear leukocytes with areas of suppurative necrosis was seen in 43 cases. In remaining four cases, epithelioid granulomas with foreign-body giant cells were seen [Figure 1b]. In four cases, vascular lumens were occluded by fungal hyphae [Figure 1b, incite]. PAS and GMS confirmed mucormycetes hyphae and they were seen as red and brown black, respectively. Prebiopsy potassium hydroxide wet mount from nasal sinuses showed mucormycosis hypha in 18 (38.29%) cases.

Reverse transcription polymerase chain reaction of throat swab for SARS-CoV-2 was negative in all patients. The duration of past COVID-19 history in all patients ranged from 7 to 25 days.

Due to varied site of involvement by mucormycosis, common complaints were swelling and pain of the nose, orbit, and face. Other complaints were nasal obstruction, watering of the eyes, fever, headache, and toothache. The two patients had drooping of one of the eyelid and one patient had fever and breathlessness.

The males (n = 31) were commonly affected than females (n = 16). The 20 (42.55%) patients were in the age

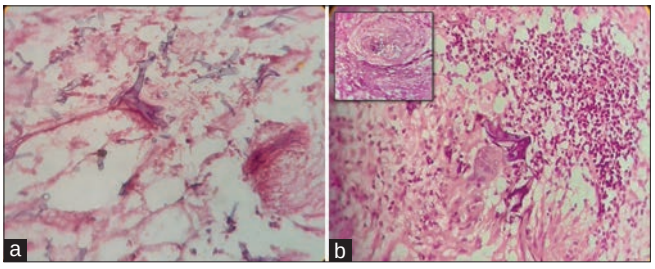

Figure 1: Nasal Sinus tissue (a) Broad, thin-walled pleomorphic nonseptate hyphae of mucormycosis (H and E, ×400). (b) Granulomatous inflammation with hyphae (H and E, ×400), vessels blocked by hyphae (Incite, H and E, ×400)

Table 1: Region, age, and sex distribution of mucormycosis in 47 patients

Site	Nose and sinuses		Nose, sinuses, and orbit		Nose, sinuses, orbit, and brain		Lung		Total, *n* (%)
	Male	Female	Male	Female	Male	Female	Male	Female	
Age sex group									
30-40	6	2	0	0	0	0	1	0	9 (19.14)
41-50	8	4	4	1	3	0	0	0	20 (42.55)
51-60	1	2	3	2	2	3	0	0	13 (27.65)
61-70	0	1	0	1	0	0	0	0	2 (4.5)
>70	2	0	1	0	0	0	0	0	3 (6.38)
Total, *n* (%)	17	9	8	4	5	3	1	0	47

group of 41–50 years followed by 13 (27.65%) in the age group of 51–60 years. The most common age group for males ($n = 15$) was 41–50 years, whereas for females ($n = 7$), it was 51–60 years [Table 1].

Out of 47 patients, 37 (78.72%) have associated diseases. The 39 patients receive steroid treatment during their COVID-19 hospital admission stay. The 29 patients were known diabetics, out which more than half ($n = 16$) patients have also associated hypertension. The two patients were having hypertension only and one patient had chronic kidney disease. The five patients at the time of COVID-19 hospitalization were diagnosed with new cases of diabetes mellitus.

Depending on the site of involvement, magnetic resonance imaging (MRI) showed mucosal thickening of paranasal sinuses which appeared as hyperintense or hypointense, deviation of nasal septum, and ill-defined hyper intensities in surrounding soft tissues. The cases in which brain parenchyma ($n = 8$) were involved showed parenchymal enhancement in the frontoparietal or cerebellar regions or in the lateral part of the pons. MRI suggested fungal infections of only paranasal sinuses (sinusitis) in 26 cases and sinusitis with involvement of orbit (Rhino-orbital) in 12 cases. The 8 cases showed involvement of sinuses, orbit and brain (Rhino-orbito-cerebral) and one case showed involvement of the lung in the form of opacity. Table 1 shows detailed age, sex, and site distribution in 47 patients of mucormycosis. Right-sided involvement of the face was seen in 22 (46.80%) patients, whereas left-sided involvement in 20 (42.55%) patients. Bilateral involvement was seen in four cases.

DISCUSSION

A complex interplay of factors in COVID-19 infections lead to secondary infections which are increasingly being recognized in view of their impact on morbidity and mortality. In recent review, 8%–10% patients had secondary bacterial or fungal infections during hospital admission.[8-12]

Various factors such as excessive use of corticosteroids for immunosuppression, uncontrolled diabetes mellitus, immunedysregulation associated with COVID-19, long-term stays in intensive care unit, hypertension, hyperferritenimic syndrome associated with COVID-19, and chronic kidney disease have been implicated in various studies.[1,5-7] In our study, all the 47 patients were diagnosed with mucormycosis and all patients gave a history of COVID-19-related admissions.

Mucormycosis is a angio-invasive disease caused by a group of molds which are called as mucormyetes and it is potentially a fatal infection if inadequately treated. It is often referred to as black fungus. These saprophytic fungi are widely distributed in nature. The infection is acquired by exposure to the sporangiospres. The disease is characterized by tissue infarction and necrosis.

Data from the previous literature indicate that the estimated prevalence of mucormycosis in India is nearly 70 times higher than global data which was estimated to be at 0.02–9.5 cases/100,000 persons.[13] Uncontrolled diabetes mellitus is the most common underlying disease associated with mucormycosis in India.[14,15]

Based on the published literature from December 2019 to start of April 2021, India has contributed to approximately 71% of the global cases of mucormycosis in patients with COVID-19.[5]

In our study, males were more commonly affected than females with maximum ($n = 33$) patients in the 4th and 5th decade. The most common age group for females (51–60 years) was more than males (41–50) [Table 1].

The 78.72% patients of mucormycosis had associated diseases. The maximum ($n = 39$) patients received steroids during their previous COVID-19 infection and 34 patients had either diabetes mellitus with hypertension or diabetes mellitus alone. The diabetes mellitus has been the single most common risk factor for mucormycosis in India in COVID-19 patients being reported in over 50% of cases.[1,14] In addition, there is strong evidence which suggest SARS-CoV-2 infection induce damage to pancreatic islets resulting in acute diabetes and diabetes ketoacidosis which

facilitates the growth of mucormycosis. The reason is that there is a high expression of angiotensin-converting enzyme-2 receptors in pancreatic islets along with increased insulin resistance due to cytokine storm.[16] Similar observations were made in our study The five diabetes mellitus patients out of 34 patients got to know during COVID-19 admission that they have diabetes mellitus.

Another possible explanation for association between COVID-19 and mucormycosis is that severe COVID-19 is a hyper-ferritinemic syndrome. High ferritin levels lead to excess intracellular iron that generates reactive-oxygen species resulting in tissue damage which facilitates the growth of fungus. Iron overload and excess free iron seen in acidemic state are one of the keys and unique risk factors for mucormycosis.[17]

Other possible explanation for the association between COVID-19 and mucormycosis is the endotheliitis observed in severe COVID-19 patients. Endothelial adhesion and penetration are the critical early steps in mucormycosis.[17,18]

One patient of mucormycosis had chronic kidney disease. Few studies from India reported that mucormycosis patients had chronic kidney disease in 9%–32% of patients.[14,15]

The three clinical forms of mucormycosis have been identified.

(1) Rhino-cerebral form which begin as fulminant infection of nasal cavity, paranasal sinuses, and soft tissue of the orbit. It is often unilateral and may extend directly to involve meninges and brain. (2) Invasive pulmonary mucormycosis and disseminated mucormycosis. (3) Cutaneous mucormycosis which is usually manifestation of disseminated mucormycosis. We came across with 46 patients of rhino-cerebral form and only one patient had pulmonary mucormycosis. Involvement of the nose, paranasal sinuses, orbit, and brain depends on the stage and severity of the disease at diagnosis.

All the patients were treated with aggressive surgical debridement of involved tissue and administration of parenteral amphotericin B. The 46 patients received parenteral amphotericin B and one patient received psoaconazole for 21 days as prescribed by physicians. In addition, all the patients received broad-spectrum antibiotics. Out of 47, the 11 (23.40%) patients underwent either of the eyeball exenteration adding substantial morbidity to post-COVID-19 disease. A very high morbidity in our study can be attributed to the advanced stage of the disease at the time of diagnosis being a tertiary care center patients were referred late for the diagnosis and treatment. Patients were referred to regional centers for follow-up.

CONCLUSION

Although severe COVID-19 disease is associated with significant incidence of secondary bacterial and fungal infections, mucormycosis appears to be the most common fungal infection in severe post-COVID-19 disease at our facility. Severe COVID-19 disease, use of steroids in treatment of COVID-19, and hyperglycemia appear to be the most common causes. Early diagnosis and treatment are the keys for reduction of morbidity and mortality which require expertise and interdisciplinary co-ordination. Cranio-fascial pain in patients with a history of severe COVID-19 disease, a mucormycosis must be suspected. The demonstration of fungi in tissue biopsy is the key for definitive diagnosis.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Short Report

Vesiculobullous variant of Darier's disease with flexural freckle-like macules: A rarer presentation of a rare disease

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Abstract The bullous variant of Darier's disease is a rare subtype and is often clinically and histologically similar to Hailey–Hailey disease (HHD). We report a case on similar lines of Darier's disease presenting with dirty warty papules and freckle-like brownish macules in flexural distribution with vesiculobullous lesions, erosion, and crusting-like HHD.

Keywords: Bullous Darier's disease, flexural freckle-like macules, Hailey-Hailey Disease

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SHORT REPORT

A 21-year-old female with no past medical history presented with hyperpigmented warty papules for the past 7 months in her axilla, groin, cubital fossa, and flaccid vesicles on her abdomen for the same period. The lesions had seasonal exacerbation during summer with friction, sweating, and humid weather being aggravating factors. Mucocutaneous examination revealed brown freckle-like macules and hyperkeratotic papules in the axilla, groin, and antecubital fossa [Figure 1a and b]. Vesicles on erythematous base, erosion, and crusting present over the lower neck, inframammary area, chest, back, and abdomen were observed [Figure 1c and d]. There were no oral mucosal or nail changes and palms and soles were within normal limits. Nikolsky's sign was negative. Further inquiry revealed no similar history in any other member of the family. Histopathology from a papule revealed hyperkeratosis, discrete intraepidermal clefts, numerous dyskeratotic cells in the form of corps ronds in the epidermis, and few acantholytic cells in the cleft [Figure 2a and b]. Histopathology from a vesicle

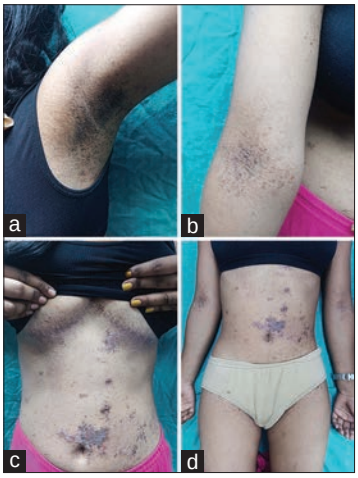

Figure 1: (a and b) Dirty, warty keratotic papules and brownish freckle-like macules over axilla and antecubital fossa, (c and d) flaccid vesiculobullous lesions, erosion and crusting over inframammary area, chest, and abdomen

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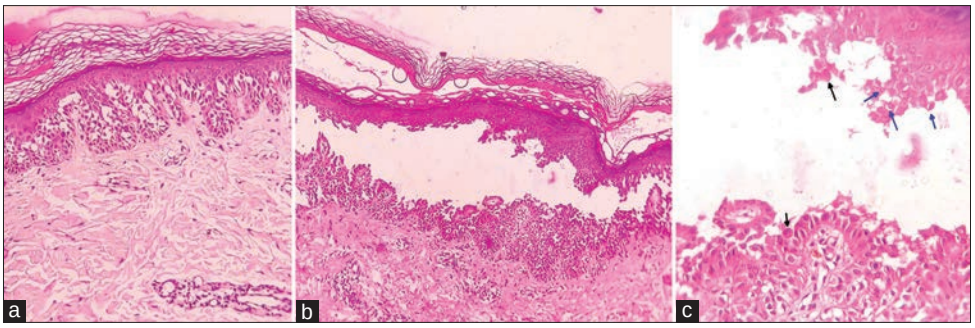

Figure 2: (a) HPE (×10 view) of papule revealing hyperkeratosis, discrete intraepidermal clefts, and marked dyskeratosis. (b) HPE (×10 view) of vesicle revealing large confluent cleft, marked dyskeratosis. (c) HPE (×40 view) of vesicle showing villi formation, acantholytic cells (black arrows,) and dyskeratotic cells (blue arrows)

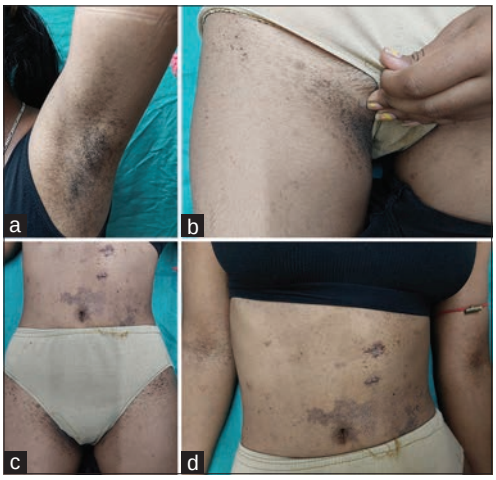

Figure 3: (a-d) Posttreatment image after 1 month of therapy showing excellent therapeutic response with isotretinoin. Brownish freckle-like flexural pigmentation remained the same

revealed similar findings except that acantholysis was more prominent in the form of large confluent clefts, upward projection of papilla projecting into the cleft lined by a single layer of basal keratinocytes (villi formation), and a "dilapidated brick wall" appearance [Figure 2c]. Direct immunofluorescence done from perilesional skin did not exhibit any immune deposits. Although there was a clinicopathological overlap between Darier's disease and Hailey–Hailey disease (HHD), our diagnosis was bullous variant of Darier's disease. We started the patient on isotretinoin 20 mg daily along with topical emollients and antimicrobial ointment applied over the eroded and crusted areas. Marked improvement was seen after 1 month, with healing of erosions and crusting and reduction in hyperkeratotic papular lesions in all the sites with residual hyperpigmentation [Figure 3a-d]. However, the brownish freckle-like macules remained unchanged.

DISCUSSION

Darier's disease is an autosomal dominantly inherited rare disorder of keratinization with complete penetrance but variable expressivity. It is caused by mutation in ATP2A2 gene which encodes sarcoplasmic/endoplasmic calcium ATPase pump and SERCA2b. This leads to Ca2+ depletion in the cell eventually resulting in acantholysis and apoptosis of keratinocytes. Clinically, it manifests in adolescence or early adulthood as dirty, warty, and crusted papules in seborrheic and intertriginous distribution with exacerbation in summers and humid weather. There may also be oral mucosal or nail involvement and flat-topped papules on dorsal hands and feet. Darier's disease may follow a chronic course and is associated with complications such as secondary infections, neuropsychiatric disorders, ocular ulcerations, and rarely squamous cell carcinomas.

Darier's disease may have rarer atypical presentations such as vesiculobullous lesions, acral hemorrhagic lesions, guttate hypopigmentation, segmental distribution, and comedonal or nodulocystic lesions.[1] Vesiculobullous lesions in Darier's disease were first reported by Pels and Goodman in 1939. Literature review shows that there are certain overlapping clinicopathological features with HHD which may cause diagnostic dilemmas.[2-4] It has also been reported to mimic bullous pemphigoid[1] and pemphigus vulgaris.[5] Vesiculation occurs due to the enlargement of microscopic intraepidermal lacunae probably precipitated by high humidity, temperature, ultraviolent radiation, and surgery or physical stress.[4]

Certain clinical findings in our patient like earlier age of onset (second decade), the presence of dirty warty keratotic papules in flexural distribution, and excellent response with oral retinoids were suggestive of Darier's disease. The presence of large confluent clefting, villi formation and "dilapidated brick wall" appearance on histology of bullous lesions pointed toward the diagnosis of HHD but marked hyperkeratosis, numerous dyskeratotic cells, and the relative paucity of acantholytic cells were more in keeping with diagnosis of bullous Darier's disease.

Genetic studies would have been definitive but it was beyond our scope.

Although vesiculobullous morphology in Darier's disease in itself is a rare presentation our case was unique in a way that there was the absence of family history, sparing of typical sites such as seborrheic areas, oral mucosa, and nails. The presence of brownish-pigmented macules in the flexural distribution has not been reported earlier.

Declaration of patient consent

The authors certify that they have obtained the appropriate patient consent form. In the form, the patient has given consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Brief Report

Small airway disease: A new "phenotype" of obstructive airway disease

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Abstract

Small airways are usually defined as noncartilaginous airways with an internal diameter <2 mm. Robust data are available regarding small airway involvement in various obstructive airway diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD). Small airway disease (SAD) can present as a starting point of emphysema, and in few cases, SAD can present with emphysema. Thus, SAD in COPD is a different phenotype along with emphysema and chronic bronchitis. Although bronchial asthma is a disease of large and medium size airways, small airway involvement has been documented in asthma in late stage. Involvement of small airways in asthma is a clinical clue toward the role of inhaled antimuscarinic therapy in this phenotype. Spirometry is a simple and cost-effective but less reliable test to diagnose SAD in comparison to impulse oscillometry. Inhalation therapy with small particle size aerosol long-acting beta-agonist plus inhaled corticosteroids is recommended for treatment of SAD. Targeting small airways in asthma and COPD with ultrafine particle-size inhaled medicines with antimuscarinic drugs will have a successful treatment outcome.

Keywords: Asthma, chronic obstructive pulmonary disease, obstructive airway disease, small airway disease, spirometry

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the second leading cause of death in India and affects almost 53 million people, respectively.[1] Various chronic respiratory diseases are common in India including COPD, asthma, bronchiectasis, interstitial lung diseases, and posttuberculosis obstructive airway diseases. The authors have observed 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 in their study in rural settings in India.[2]

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Hogg *et al.* in 1968 first used the term small airway disease to describe airway disease in patients with variably severe chronic airflow obstruction characterized by loss of bronchioles, mucus plugs, and variable amounts of inflammation and fibrosis that involve "the smallest bronchi as well as the bronchioles, so that neither bronchitis nor bronchiolitis is an appropriate term."[3] This can reduce airway patency and render the airways more liable to collapse upon expiration. Overall, these changes can reduce airflow, increase gas trapping and thus reduce ventilatory capacity. Disease severity was noted to correlate with

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occlusion of airway lumen by mucus and inflammatory cells. Small airway disease (SAD) is a key feature of COPD, and has been studied extensively over many decades. The small airways have been defined as <2 mm diameter and arise from the 4th to 13th generation of airway branching (taking trachea as 1st generation to alveoli as 23rd, but on average arise by the 8th. Also known as peripheral airways, the small airways (<2 mm in diameter) include bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar sacs [Figure 1].[4,5] The narrow diameter of the peripheral airways means that particles can more easily collide with the surface and cause damage compared to the larger airways. Small airways are not easily visualized by imaging techniques and their histopathological analysis is best analyzed in surgical lung biopsies because bronchoscopic transbronchial biopsies usually contain only a few small airways. The difficulties of sampling these airways in human subjects are responsible for the limited recognition of the important pathophysiological roles of small airways, which have been called the "silent zone."

It is estimated that 20% of small airways below 2 mm diameter comprise bronchi with elements of cartilage within their walls, while the remainder are bronchioles or alveolar ductal spaces.[6] More recently, the role of small airway disease in the pathogenesis of COPD has been recognized by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[7]

ISSUES NEED FURTHER EVALUATION IN CASES WITH SMALL AIRWAY DISEASE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Small airway disease in chronic obstructive pulmonary disease pathophysiology

COPD is attributed to long-term exposure to toxic gases and particles, most often related to cigarette smoking. The primary host defenses against this stimulus are the innate and adaptive inflammatory immune responses. The innate defense system of the lung includes the mucociliary clearance system and the epithelial barrier, supported by the acute inflammatory response that follows tissue injury. The repair process associated with both types of response remodels damaged tissue by restoring the epithelium and microvasculature and adding connective-tissue matrix in an attempt to return the tissue to its previous state. The multivariate analysis indicates that progression of COPD from GOLD stage 0 to GOLD stage 4 was most strongly associated with thickening of the airway wall and each of its compartments by a repair or remodeling process.[8]

Hypersecretion of mucus is the defining feature of chronic bronchitis and is associated with an inflammatory process involving the epithelium, gland ducts, and glands of the larger central airways. Although the accumulation of inflammatory exudates in the small airway lumen might be attributed to the extension of chronic bronchitis into the small airways, several studies suggest that this is not the case. At least two large clinical trials have shown that the presence of chronic bronchitis does not predict the development of airflow limitation, and pathological studies indicate that central and peripheral airway inflammation can occur quite independently of each other. Collectively, these data suggest that the cough and sputum production that defines chronic bronchitis is independent of the disease process in the small airways that are responsible for airway obstruction in patients with COPD.[8-10]

In COPD, small airway disease is characterized by airway remodeling, mucus plugging, and immune cell infiltration[5,9] [Figure 2].

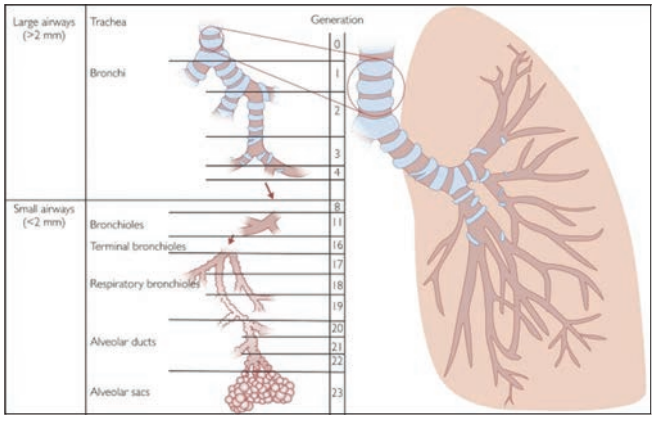

Figure 1: Small airways in the respiratory system

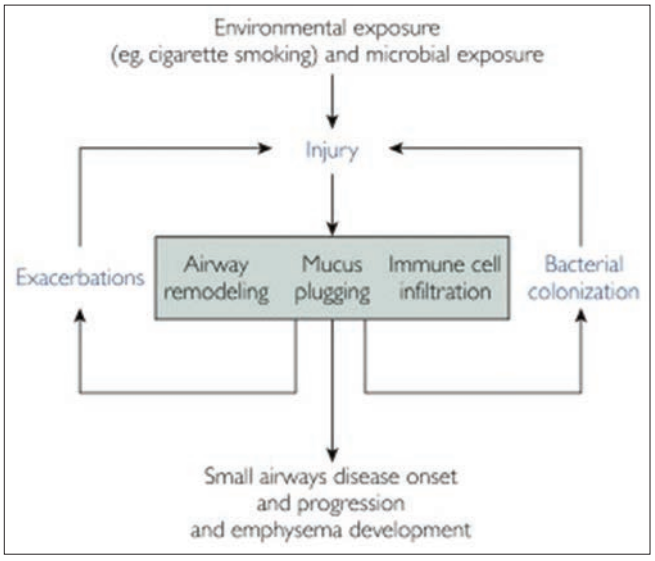

Figure 2: Pathological abnormalities associated with small airway disease

Studies have documented that obstruction of the small airways in COPD is associated with a thickening of the airway wall by means of a remodeling process related to tissue repair and a malfunction of the mucociliary clearance apparatus of the innate host defense system, which results in the accumulation of inflammatory exudates in the lumen. They have also noted that colonization and infection of the lower airways are associated with an adaptive immune response that accounts for the increase in lymphocytes and their organization into lymphoid follicles in patients with severe (GOLD stage 3) and very severe (GOLD stage 4) COPD.[8]

Early change in chronic obstructive pulmonary disease or precursor of emphysema

Small airway disease is often evident before the onset of symptoms or changes in spirometry or imaging findings in COPD. The small airways represent a "silent zone" in the normal lung in which defects can accumulate without being noticed; this finding has led to the development of specialized tests to detect early abnormalities in the hope of preventing or delaying disease progression. However, traditional imaging techniques may not be sufficiently sensitive to identify the early stages of small airway disease or to differentiate between the contribution of small airway disease and emphysema. Because extensive small airway damage and obliteration can occur before it is detectable with conventional spirometric tests, spirometry is also of limited use as a screening tool for early disease.[11,12]

Small airway disease may be a precursor to emphysema. Very severe COPD is associated with a marked reduction in both the number of terminal bronchioles and the minimal lumen caliber of those that remain these changes can be present in regions of the lungs not yet affected by emphysema, suggesting that they may begin at very early stages in the natural history of COPD. Other studies have reported that both small airway disease and emphysema are associated with decline in forced expiratory volume in 1 s (FEV1), but small airway disease has a greater role in the decline associated with mild-to-moderate airflow limitation, which indicates a role early in the disease course.[13-16]

Effect of small airway disease on hyperinflation

Pulmonary hyperinflation is a common cause of dyspnea and functional limitation in patients with COPD. Small airway disease can lead to expiratory flow limitation, gas trapping within the lung, and dynamic hyperinflation. This is characterized by flattening of the diaphragm, sternal bowing, chest kyphosis, and enlarged intercostal spaces, resulting in a barrel chest. Dynamic hyperinflation develops as a result of expiratory airflow limitation coupled with decreased exhalation time, for example, during exercise, and is associated with decreased inspiratory capacity and increased functional residual capacity.[17-19]

Hyperinflation affects clinical outcomes in COPD; for example, activity-related dyspnea associated with hyperinflation can lead to a vicious cycle of activity avoidance, physical deconditioning, and reduced health-related quality of life. Indeed, dynamic hyperinflation and exercise limitation are both independent predictors of mortality in patients with COPD. Hyperinflation also has implications for the early development of comorbidities such as cardiovascular disease. Of particular concern, hyperinflation impairs the mechanical function of the respiratory muscles and has adverse effects on the cardiocirculatory system.[17-19]

Spirometry when forced expiratory volume in 1 s is normal or forced expiratory volume in 1 s/forced vital capacity preserved

Small airway disease can be difficult to assess because of the small size and inaccessibility of the airways. With small airway disease, traditional lung function tests may only become abnormal once there is a significant burden of disease.[12] Hence, although spirometry is the gold standard for diagnosing COPD, FEV1 is not an adequate measure of small airway disease.[6,11] Small airway disease is associated with bronchodilator responsiveness in terms of volume (forced vital capacity [FVC]) but not in terms of flow (FEV1).[20] Indeed, FVC has been used as an indirect measure of small airway disease in several clinical trials.[21]

Forced expiratory flow (FEF) between 25% and 75% of the FVC is another common measure of small airway abnormality, though there is conflicting evidence regarding its reliability. Other measures of expiratory flow include evaluation of maximal expiratory flow when 75%, 50%, or 25% of FVC remains.[11,12] The ratio of FEV3/FEV6 has also emerged as an earlier and more sensitive marker of small airway disease compared with other spirometric measures, with low FEV3/FEV6 found to be associated with impaired computed tomography (CT) scanning measures of small airway disease in patients with normal FEV1/FVC.[22]

Diffusing capacity for carbon monoxide (also known as a transfer factor of the lung for carbon monoxide), which indirectly measures the degree of gas transfer from alveoli to pulmonary capillary blood, has also been found to correlate with small airway disease.[23] The forced oscillation technique (FOT) and impulse oscillometry (IOS) are techniques that can be used to determine the mechanical

properties of the lung.[11,12] The FOT and IOS work by applying oscillating pressure variations of varying frequencies to the lung during normal tidal breathing, with the resulting pressure and flow changes measured at the mouth. High-frequency signals reflect the contribution of larger airways, whereas low frequencies reflect the whole lung; as such, the contribution of the small airways can be found by comparing the two.[12] Inert gas washout techniques such as the single-breath nitrogen washout test and multiple-breath nitrogen washout (MBN2W) test may also be used to assess small airway disease. These techniques work by measuring the efficiency of gas mixing in the lungs, which varies according to the structure of the large and small airways and can therefore give an indication of small airway disease.[11,12]

ISSUES NEED FURTHER EVALUATION IN CASES WITH SMALL AIRWAY DISEASE AND ASTHMA

Small airway disease in asthma

Asthma was originally described as an inflammatory disease that predominantly involves the central airways. Pathological and physiological evidence reported during the past few years suggests that the inflammatory process extends beyond the central airways to the peripheral airways and the lung parenchyma. Most of the evidence derives from invasive historical pathological studies that collected lung tissues from autopsied patients or from subjects with asthma needing lung resection because of malignancy, as well as from data on patients undergoing transbronchial biopsies.[24] Small airways are thickened in asthma due to chronic inflammation in the epithelium, submucosa, and muscle area.[25] It has been suggested that the outer wall is more inflamed than the inner wall, with a higher number of lymphocytes, eosinophils, and neutrophils associated with an increased mRNA expression of interleukin (IL)-4, IL-5, and eotaxin.[26] The latter may contribute to an uncoupling of the small airways with the surrounding lung parenchyma increasing their collapsibility. Some investigations suggest that the cellular infiltrate increases toward the periphery, while others show different patterns. These contradictory data may be ascribed to the heterogeneity of asthma and to the different methods adopted in the studies.[27,28] Abnormal acinar ventilation heterogeneity has also been reported to be present despite mild symptoms and normal spirometry, supporting the role of small airways as an early marker of disease.[29]

An important question is whether small airway involvement in asthma is variable among distinct asthma phenotypes or whether it occurs in all patients. Cluster analyses have been recently used to identify specific asthma phenotypes,[30] but markers of small airway function have not been investigated. However, evidence is accumulating to support the concept that small airway dysfunction and inflammation may contribute to distinct asthma phenotypes. Kraft *et al*. reported that patients with nocturnal asthma had a significantly greater number of eosinophils in the small airways compared with the proximal airways in biopsies undertaken during the night. In addition, eosinophil and macrophage counts were increased in biopsies of their distal airways undertaken at night compared with those taken in the afternoon.[31] Furthermore, in a follow-up study performed by the same group, it was reported that patients with nocturnal asthma showed significantly increased peripheral airway resistance compared with those with nonnocturnal asthma[32] Identification of pathologic changes in early and mild obstructive lung disease has shown the importance of the small airways and their contribution to symptoms. Indeed, significant small airway dysfunction has been found prior to any overt airway obstruction being detectable by conventional spirometry techniques.

Small airway disease and degree of control of asthma

One of the main long-term goals of asthma management is to achieve a good disease control, by repeatedly reviewing patient's symptoms (daytime symptoms, nocturnal symptoms, activity limitations, and use of rescue medications) and future risk of exacerbation, adverse effect of therapy and lung function decline, and by adjusting the treatment accordingly. Current recommendations are therefore based on the level of asthma control rather than disease severity. Available data in randomised controlled trials showed asthma control is achievable with available inhaled medicines. Real life studies in last 20 year have observed large proportion of asthmatics are under controlled either due to noncompliance or irrational treatments offered to patients.[30-33] A more robust amount of data relates to the clinical course and the degree of control of asthma with small airway disease. van Veen *et al*. found that exhaled NO predicts lung function decline in patients with severe asthma during 5 years of prospective follow-up.[34] Interestingly, this relationship was only observed in subjects with baseline FEV1 >80% predicted, suggesting that these findings may be related to small rather than larger airways. This supports the notion that conventional spirometric methods of assessing airway function in the clinic cannot reliably and sensitively evaluate small airway dysfunction.

Bourdin *et al*. reported that patients with asthma and a history of two or more exacerbations per year had a significant increase in the slope of phase III nitrogen washout.[35]

However, since this study had a cross-sectional design, it is unclear whether this represents simply an association or whether abnormalities in small airways may be considered a predictive marker of subsequent exacerbations. In a further trial, a group of patients with asthma and recurrent exacerbations (at least two exacerbations in the previous year) were compared with a group of subjects with equally severe but well-controlled asthma. The authors reported that patients with asthma who had recurrent exacerbations had increased closing volume (CV) and closing capacity (CC) compared with controls, even after bronchodilation.[36] Scichilone *et al*. have shown that the alveolar component of exhaled NO was associated with a lack of asthma control in 78 patients with mild, untreated asthma.[37] Similar results were reported in patients with acute severe asthma by Thompson *et al*., who showed a direct correlation between functional abnormality in the acinar zone and airflow obstruction, degree of asthma control, and treatment requirement.[38] It has also been reported that peripheral airway function assessed by IOS significantly contributes not only to the level of asthma control but also to patients' quality of life and perception of symptoms.[39] Patients with severe asthma have more neutrophils in the lung parenchyma and display more extensive air trapping, as measured with quantitative CT scanning, indicating small airway disease.[40] More thickened small airways and a higher number of eosinophils are detectable in subjects with fatal asthma, who also exhibit more goblet cells and neutrophils when affected by a disease of short duration, suggesting that the underlying inflammatory process is also present in the distal airways.[41]

Small airway involvement has been also implicated in the onset and severity of exercise-induced bronchoconstriction. Kaminsky *et al*. challenged patients with asthma with dry cool air and observed, using a wedged bronchoscope, that there was a significant postchallenge increase in peripheral airway resistance in patients with mild asthma compared with healthy subjects.[42] It has also been found that hyperventilation increased urinary levels of CC16 proteins which, being produced by epithelial cells in the bronchiole, may act as a biomarker for peripheral airways. Abnormalities within small airways, associated with some degree of air trapping, may lead to delayed emptying of the peripheral airways during exercise and this may contribute to the frequently observed phenomenon of dynamic hyperinflation.[43]

DIAGNOSTIC TECHNIQUES FOR SMALL AIRWAY DISEASE

Spirometry

The correlation between conventional lung function measurement (FEV1 and PEF) and asthma symptoms is weak. This may be due to an airflow dysfunction in the small airways that are not reflected in the FEV1 responses. The mean FEF between 25% and 75% of FVC (FEF25-75%) is the traditional index of spirometry to assess peripheral airway obstruction in routine clinical practice.[44-47]

Some studies suggest that FEF25-75% associates with worse asthma control and poor asthma outcomes. Siroux *et al*. showed that small airway obstruction, as assessed based on FEF25-75%, might contribute to the long-term persistence of asthma and the subsequent risk for poor asthma outcomes independently from effects of the large airways.[48] Riley *et al*. showed that FEV1, FEV1/FVC, and a reduced FEF25-75% were independently associated features of more severe asthma, in patients with severe disease.[49] Despite this, the value of FEF25-75% as a predictor of peripheral obstruction has also been questioned by several studies, therefore limiting its reliability for SAD.[50]

High-resolution computerized tomography (HRCT thorax)

Lung imaging is an increasing area of interest that has been utilized for the assessment of small airway involvement in asthma and COPD and that deserves consideration. High-resolution computerized tomography (HRCT) is a noninvasive method that may provide anatomical details of the bronchial tree. However, HRCT can only estimate the wall thickness of bronchi that are 1–2 mm in diameter.[51] Although this only partially allows a direct assessment of small airway abnormalities, air trapping and ventilation heterogeneity have been quantified to indirectly support small airway functional parameters.[52] Further studies also suggest that HRCT parameters of air trapping can be selectively modified by inhaled and systemic pharmacological treatments.[53]

Multiple-breath washout techniques

The MBN2W test involves inhalation of 100% oxygen to wash out resident airway nitrogen gas during tidal breathing and it is highly reproducible.[54,55] The rate and extent of nitrogen exhalation from the tracheobronchial tree allow an assessment of ventilation heterogeneity in the lungs, distinguishing between the contribution from the proximal conducting airway compartments and that from the distal acinar regions in both asthma and COPD.[56,57] Different studies from independent groups showed that ventilation distribution was abnormal in a remarkable proportion of asthmatic patients, of whom only a fraction had an abnormal FEV1, and ventilation alterations were associated with worse asthma control, exacerbations, and higher inhaled corticosteroid (ICS) dose.[35,58,59]

Single-breath nitrogen (N2) washout test

The single-breath nitrogen (N2) washout test allows one to distinguish between ventilation heterogeneity originating in the peripheral airways versus that in the more proximal conducting airways. Gas distribution in the lungs is analyzed by measuring the change in N2 concentration during the expiration phase of a vital capacity maneuver, following a single breath of 100% oxygen. Measurements that can be undertaken include CC, CV, the nitrogen slope of phase III, and lung volumes, and it has been shown that an increased CV or CC reflects air trapping due to small airway narrowing or closure.[60]

Impulse oscillometry

The FOT was first described by DuBois in 1957 as a method to characterize respiratory impedance. The device generates sinusoidal sound waves that are transmitted into the respiratory system during quiet breathing. The modified method, IOS, was developed by Michaelson in 1976 and commercialized by Jaeger in the 90s. IOS operates by delivering a continuous spectrum of frequencies. Similar to FOT, the IOS technique uses pressure pulses delivered into the respiratory system, causing a flow reaction, but pressure oscillations in IOS in contrast to FOT are delivered to the respiratory system at a constant frequency (square waves) of 5 Hz, from which all other frequencies of interest are mathematically extracted.[33]

IOS is a simple and noninvasive method, requiring minimal patient cooperation, without the need for a shutter, body plethysmography cabin, or measurement gases. Patients can comply better with tidal breathing, compared to maximal inspiratory and expiratory maneuvers, allowing measurements in patients groups who would struggle using conventional methods, requiring forced expiratory maneuvers that can be difficult or sometimes even impossible to perform. IOS is more suitable than conventional spirometry in children under the age of 5 and in geriatric cases. IOS is a very important tool in lung function assessment in patients with obesity, patients with limitations of their respiratory drive, severe diseased patients and patients with neuromuscular abnormalities. For instance, in a study comparing oscillometry and spirometry in patients 65 and older, all were capable of producing a valid oscillometry test whereas valid spirometry was completed in only 33.4% of the participants.[61]

IOS generates oscillating pressure-flow signals of air during tidal breathing to determine central and peripheral lung mechanical parameters, such as resistance ®, reactance (X), and impedance (Z).[62] An increasing number of studies suggest that IOS measurements could be useful in the diagnosis of obstructive lung disease.[63] Both IOS and MBN2W may be used not only to assess functional abnormalities in the small airways but also to longitudinally monitor the effects of interventions and pharmacological treatments.[55,64] Respiratory resistances at 5 and 20 Hz are used as indices of total and proximal airway resistance, respectively. Thus, the contribution of the distal airways is determined by the fall in resistance from 5 to 20 Hz that is considered to be an index for the resistance of peripheral airways. IOS supports individualized patient management, independent of other functional examinations or as part of additional diagnostic measurements.[33] Interestingly, the ATALANTIS study identified R5–R20 as the IOS-measured marker that, among several small airway physiological markers, most strongly correlated with SAD.[65] Other studies showed that R5–R20 reflects small airway narrowing.[66,67] Another group showed that small airway ventilation heterogeneity captured by IOS-derived R5–R20 values is associated with CT density gradient reversal at the lung base, likely a direct consequence of SAD.[68] Manoharan *et al*. evaluated adult asthmatics with a preserved FEV1 (>80% predicted), and showed that SAD assessed by FEF25-75%, and R5–R20 was associated with a significantly increased likelihood of having worse long-term asthma control.[69]

TREATMENT OF SMALL AIRWAY DISEASE WITH SMALL PARTICLE SIZE VERSUS CONVENTIONAL PARTICLE SIZE INHALERS

Although evidence from clinical trials on treatment targeted to the small airways is mixed, "real-life" research has shown potential benefits on asthma control and quality of life and reported that corticosteroid dose can be significantly reduced with small particles and achieve as good as an effect as large particles.[70] Fundamentally, the efficacy of any topical inhaled medication is dependent upon successful distribution of the drug to the site of disease. Most inhaled therapies do not sufficiently reach the small airways, and this inability to reach and treat the peripheral airways may strongly contribute to the lack of efficacy of inhaled treatments. Pulmonary distribution of medication is impacted by the size of the inhaled particle, measured in mass median aerodynamic diameter (MMAD).. Fine ICS particles are defined as MMAD ≥2 μ in diameter and <5 μ, and are the product of inhaled therapy utilizing either a dry powder inhaler or a hydrofluoroalkane (HFA)-propelled suspension delivered via a metered dose inhaler (MDI). Extra-fine particle-sized HFA solutions, with MMAD of <2 μ delivered via MDI, have been more recently developed and are licensed for use internationally, however,

with variable approval for treatment of individuals 5–12 years of age.[33]

Therefore, involvement of distal airways in asthma and COPD has justified research efforts to create pharmacologic treatments and technologies that can reach and target the peripheral airways, i.e., extra-fine inhaled formulations. Extra-fine formulations, with a mass median aerodynamic diameter (MMAD) of approximately 1–1.5 μm, have a higher lung deposition (50%–60%) than coarse particle ICSs with an MMAD of 3–4 μm (10%–20%) and then penetrate more deeply into the peripheral airways than drugs delivered via traditional inhalers.[71,72] Importantly, small particle aerosols are not exhaled to any significantly greater level compared to large-particle aerosols, when assessed using *in vivo* lung deposition studies.[73] The authors have documented that only 16.3% of patients with SAD were treated with inhaled extra-fine therapy compared to 60.4% of patients without SAD.[33]

Evidence is growing in support of the concept that the airway dysfunction and inflammation in the small airway region of the lung may be contributing to distinct patient phenotypes. Besides the well-known concept that nonneuronal acetylcholine plays a relevant inflammatory role, the muscarinic receptor antagonism of nonneuronal acetylcholine released from airway epithelium is also important, thus potentially contributing to glycopyrronium bromide (GB) effects at level of small airways. GB has proven to be capable of inducing favorable effects on lung hyperinflation and its functional and clinical consequences, with a decrease in dyspnea and an increase in exercise capacity.[74,75]

CONCLUSION

SAD is more common in clinical scenario presenting with obstructive airway disease. SAD is considered "different phenotype of obstructive airway disease" and considered "meeting point" in asthma and COPD. SAD starts early in course of COPD and occurs late in asthma due to different pathophysiology of these common obstructive airway diseases and is labeled as "transit" for common obstructive airway disease.

SAD in COPD is "small airway phenotype" and prompt workup to evaluate by means of IOS as spirometry is less reliable and impulsive oscillometry is the best test to assess SAD. COPD cases with poor symptom control and repeated exacerbation need SAD workup and treatment accordingly. Glycopyrronium has added advantage in these cases in controlling SAD.

SAD is common in asthma patients, especially those cases with severe category, uncontrolled type, history of recurrent exacerbations, nocturnal phenotype, and cases with exercise-induced bronchoconstriction. Proportionate number of Asthma cases with additional SAD will benefit from inhaled long acting antimuscarinic therapy with Tiotropium. Rational would-be reversal of cholinergic tone with LAMA in SAD with Asthma.

SAD treatment should include small particle size or ultrafine particle size inhalers associated with asthma and COPD. Thus, SAD is a treatable phenotype of obstructive airway disease and documented satisfactory symptom control and decrease in exacerbation with improvement in quality of life in asthma and COPD.

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There are no conflicts of interest.

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Case Report

Dysphagia in a young girl: A rare cause

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Abstract

The lingual thyroid (LT) gland is a rare clinical entity due to the failure of the thyroid gland to descend to its normal cervical location during embryogenesis. The presence of an ectopic thyroid gland located at the base of the tongue may present with symptoms such as dysphagia, dysphonia, upper airway obstruction, or even hemorrhage at any time from infancy through adulthood. The incidence of ectopic LT gland is reported as 1:100,000. It is more common in females. Most of the presentations are due to oropharyngeal obstruction, including dysphagia, dyspnea, and dysphonia. Investigations include thyroid function tests, neck ultrasonography, technetium scanning, computed tomography scan, or magnetic resonance imaging. We present the case of a 5-year-old girl who presented with LT and hypothyroidism treated with levothyroxine supplementation, planned for elective surgical resection.

Keywords: Dysphagia, ectopic, lingual, thyroid

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INTRODUCTION

The lingual thyroid (LT) gland is a rare clinical entity which was found to occur due to the failure of the thyroid gland to descend to its normal cervical location during embryogenesis.[1] The presence of an ectopic thyroid gland located at the base of the tongue may present with symptoms such as dysphagia, dysphonia, upper airway obstruction, or even hemorrhage at any time from infancy through adulthood.[2]

CASE REPORT

We present the case of a 5-year-old girl who was referred to our outpatient clinic with complaints of progressive dysphagia and odynophagia. Her past medical history was insignificant. There were no symptoms of hypothyroidism. The scholastic performance was also good. Her mother denied receiving any medications during pregnancy.

On physical examination, it was noticed that she had a 3 cm × 3 cm midline smooth, vascular, and reddish mass at the base of the tongue [Figure 1a]. A neck examination revealed neither a palpable thyroid gland nor any other palpable masses. The child was 101 cm tall which was – a 1 standard deviation score for age and gender.

Thyroid function test was suggestive of primary hypothyroidism with a thyroid-stimulating hormone of 51.4mIU/l and free L-thyroxine of 0.9 μg/dl. Other laboratory tests were within normal limits. Thyroid sonography revealed an absent thyroid gland at the eutopic location and subsequent technetium-99m (Tc-99m) thyroid

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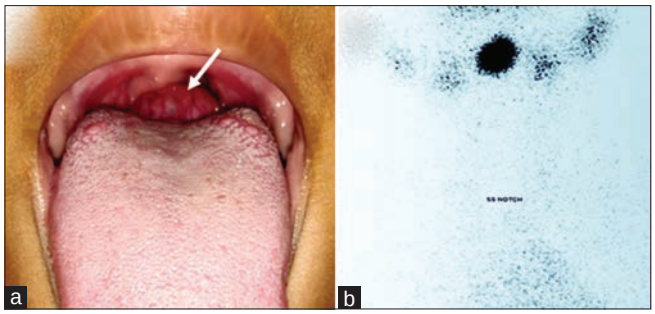

Figure 1: (a) Picture of the lingual thyroid in the respective case. (b) 99m-technetium radionuclide scan revealing the increased tracer uptake in the buccal position and absence in the eutopic position of the thyroid

scan done few months later, revealed isotope uptake at the base of the tongue and no uptake in the normal thyroid location [Figure 1b]. Washout of Tc-99m was prompt and with no focal retention. The bone age was 4 years.

The final diagnosis was ectopic LT with primary hypothyroidism. She was started on thyroxine supplementation with weight-based dosing. An option of surgical management is further planned when she becomes euthyroid.

DISCUSSION

In 1869, the first case of LT was recorded by Hickmann. Later, Montgomery stressed that for a condition to be branded as LT, thyroid follicles should be demonstrated histopathologically in tissues sampled from the lesion.[3] The thyroid gland appears as endodermal proliferation in the pharyngeal floor between tuberculum impar and hypobranchial eminence (later becomes the foramen cecum), to descend later from the foramen cecum in the tongue, passes the hyoid bone, to the final position in front and lateral to the second, third, and fourth tracheal rings by 7 weeks of gestation. During this descent, thyroid tissue retains its communication with the foramen cecum, known as the thyroglossal duct, which degenerates once the thyroid reaches the final position. This descent may arrest anywhere along this path and may remain unnoticed until puberty. Any functioning thyroid tissue found outside of the normal thyroid location is termed ectopic thyroid tissue.[4] Although ectopic tissue is usually found along the normal path of development, it has also been noted in the mediastinum, heart, esophagus, and diaphragm. LT is the result of the failure of descent of the thyroid anlage from the foramen cecum of the tongue. The reasons for the failure of descent are unknown.[5]The surface of the lesion is usually smooth and vascularity can be seen. Often, the increasing demand for thyroid hormone as the child grows may not be met by the ectopic thyroid tissue, which may lead to its enlargement causing the symptoms. This was the case in our patient. A thorough head-and-neck examination with special attention to the base of the tongue is mandatory. Palpation of the neck is extremely essential, to check the presence or the absence of the thyroid gland in its normal position. Investigations including thyroid function tests and technetium scanning confirm the presence of ectopic thyroid tissue at the base of the tongue. There was no normal thyroid gland on scintigraphy and radiological examinations in our case. The treatment options for LT include levothyroxine therapy, radioactive iodine ablation, and LT ectomy.[4]

CONCLUSION

LT is a rare anomaly representing faulty migration of the normal thyroid gland. The exact pathogenesis of this ectopic is not known. It is seven times higher in females. Dysphagia and dysphonia are common presenting symptoms. A thorough head-and-neck examination with special attention to the base of the tongue is essential. The investigation includes thyroid function tests, neck ultrasound scan, technetium scanning, and contrast-enhanced magnetic resonance imaging scan. Fine-needle aspiration cytology is not preferred by some authors as it would cause unnecessary bleeding.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Cystadenoma of seminal vesicle

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Abstract

Benign cystadenomas are the rarest tumors of the seminal vesicles (SVs). Only 22 cases of cystadenoma of the SVs have been noted till now. Clinical findings and imaging studies are nonspecific so the diagnosis is made on the final pathology. The only curative treatment is surgical resection. We report the case of a SV cystadenoma in a 65-year-old male presented with lower urinary tract symptoms, on imaging cystic mass was seen in the rectovesical space. Pathological examination after excision of the mass has confirmed the nature of a benign cystadenoma of the SV.

Keywords: Benign seminal vesicle tumor, cystadenoma, seminal vesicles

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INTRODUCTION

The seminal vesicles (SVs) are paired organs that are located posteriorly to the bladder and prostate. A SV has a capacity of around 4 ml and a length of 5–7 cm. The secretions of SV make up 80% of seminal fluid.[1] Primary tumors of the SVs are very rare and could be benign or malignant, and benign tumors, such as cystadenomas are rarer than malignant ones. They are usually present in the second and third decades of life. High-resolution transrectal ultrasonography (TRUS)-guided biopsy can be useful for assisting the diagnosis. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are more useful techniques to characterize the lesion of the SV.[1] As these tumors are rare, there is no definitive treatment protocol defined for their management.[2] We report a rare case of a benign cystadenoma of the SV.

CASE REPORT

A 65-year-old male presented with complaints of burning micturition and lower urinary tract symptoms for 3 years. He developed acute urinary retention 6 months ago. Physical examination was unremarkable, digital rectal examination revealed grade 3 prostatomegaly, firm in consistency, nonnodular, and nontender, his serum PSA was 26.13 ng/ml. Ultrasonogram revealed, cystic mass of 120 mm × 86 mm noted adjacent to the prostate with internal nodule of size 61 mm × 53 mm and prostate volume was 73 cc. TRUS biopsy was done and showed benign prostatic hyperplasia. Ultrasonography (USG)-guided fluid aspirated from cystic mass showed no malignant cells. Hematological and renal biochemical parameters are normal with a normoglycemic status. MRI of pelvis well-defined T1 hypointense and T2 hyperintense cystic lesion of size 136 mm × 96 mm with a T2 hyperintense eccentric soft tissue component of size 56 mm × 52 mm noted in the rectovesical space with any perilesional fat stranding compressing bladder and prostate [Figure 1]. On the basis

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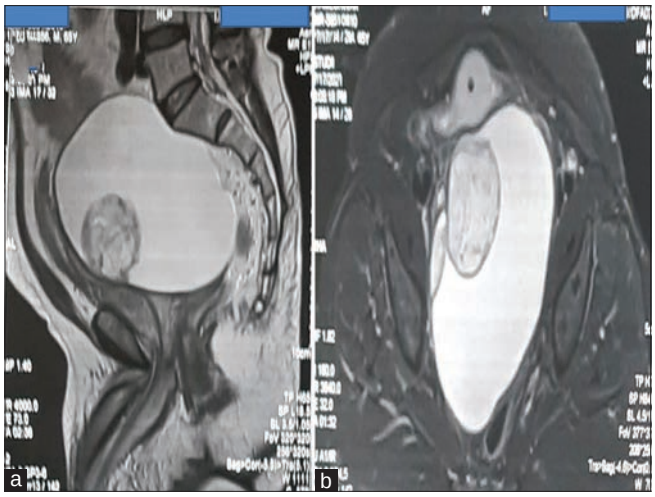

Figure 1: Well-defined T1 hypointense and T2 hyperintense cystic lesion of size 136 mm × 96 mm with a T2 hyperintense eccentric soft tissue component of size 56 mm × 52 mm noted in rectovesical space (a) sagittal section, (b) on a cross-section

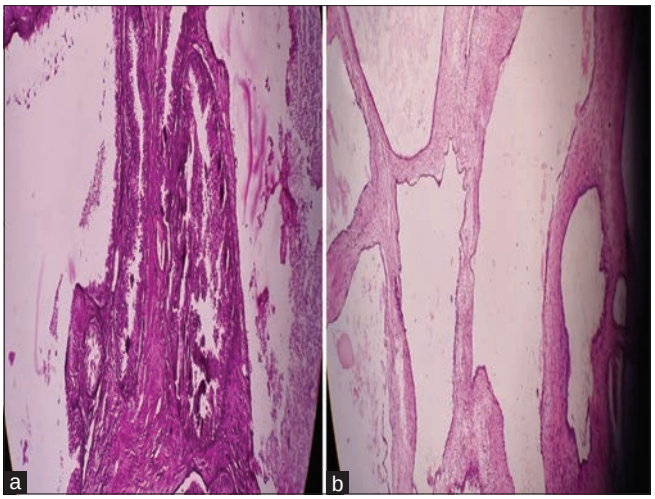

Figure 2: (a) Higher magnification of cystadenoma arising in the seminal vesicle, (b) lower magnification of cribriform and papillary growth pattern

of the above investigations, the diagnosis of rectovesical space-occupying lesion was explored by transperitoneal approach. Intraoperatively, large 10 cm × 12 cm cystic SOL in rectovesical space, densely adherent with posterior wall of bladder, seminal vesicle, and anterior wall of the rectum. Intraoperative USG confirmed 6 cm × 6 cm solid component originating from the posterior wall of the urinary bladder. Excision of cystic mass done and specimen sent for histopathological examination (HPE).

Microscopic findings included cystic spaces lined by flattened epithelia with focal nuclear stratification and focal papillary infoldings projecting into cystic spaces, tumor cells have pale eosinophilic cytoplasm, a round-to-ovoid nucleus with bland nuclear chromatin and inconspicuous nucleoli, no significant pleomorphism, mitosis, or necrosis noted. All the above features on the histopathology pointed toward a benign pathology, papillary serous cystadenoma of SV [Figure 2].

Patient with on 6-month follow-up doing well.

DISCUSSION

SVs, originate from Wolffian (mesonephric) duct during embryogenesis. Among all tumors of the SV, benign primary tumors including cystadenomas are the rarest ones.[3] Other neoplasms include fibromas, leiomyosarcomas, schwannomas, and papillary adenomas.

The unilateral nature of tumor favors its primary origin.[1] SV cystadenoma is a mixed epithelial stromal tumor of the SV. This tumor originates from the embryological residues of the Müllerien ducts. It was first reported in 1951. Cystadenomas of the SV typically occur in middle-aged and elderly men. They are almost never bilateral. The diagnosis is typically made on the final pathology after surgical resection.[4] In the English literature, about 23 cases of cystadenoma of the SV have been reported since 1944. The median age of reported cases was 48. Different symptoms were described by patients such as lower abdominal pain, hematospermia, lower urinary tract symptoms, dysuria, and hematuria. In some cases, no symptoms were recorded.[5] Occasionally, infertility is the main feature. In most cases, the diagnosis is obtained in adults in the third decades of life.[6] The median diameter of the reported tumors was 8.8 cm. The follow-up varied between different cases and recurrence was reported in two cases. USG is considered an important screening test since it is convenient, fast, and presents no risk of radiation. The second important screening tool is enhanced CT, allowing the determination of the nature of the tumor. MRI accurately defines the anatomic relationships of the tumor and is seems useful for surgical planning.[5] The clear boundaries of the lesion, the regular shape, and the absence of infiltration provide evidence of a benign behavior of the lesion.[7] Histopathological characterization of the tumor could be obtained through TRUS-guided focused biopsies before surgery.[5] These results can be explained by the predominant cystic nature of the lesion. Histologically, cystadenoma of the SV is made of cysts, of varying numbers, sizes, and shapes. These cystic lumens are surrounded by fibrous or fibromuscular connective tissue.[8] A single layer of cuboidal epithelium lines the cystic spaces.[3]

There is no standard surgical approach for these tumors due to their rarity. The only curative treatment is surgical

resection, either by open or laparoscopic surgery. Although open surgery is the approach of choice, open surgical techniques include transperineal, transvesical, paravesical, retrovesical, and transcoccygeal approaches. Transperitoneal laparoscopic vesiculectomy for SV cystadenoma was recently increasingly performed. The oncological outcomes are wonderful and the recovery after surgery is relatively fast.[9]

CONCLUSION

We report a case of cystadenoma of SV in a 65-year-old patient. Benign primary tumors including cystadenomas are the rarest ones. The diagnosis is typically made on the final pathology. The only curative treatment is surgical resection, either by open or laparoscopic surgery.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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"Pooping duck" sign

A 25-year-old male patient presented with an accidental fall on the ground, leading to acute left wrist pain and swelling. Radiographs showed no significant bony injury except a small cortical fleck of bone noted on lateral projection over the dorsal surface of the carpals [Figure 1a]. Computerized tomography (CT) scan was advised and confirmed dorsal cortical fracture of triquetrum and the avulsed fragment lying dorsal to it [Figure 1b]. Rest of the carpal bones had normal alignment with no fracture. The characteristic radiographic feature, in the lateral radiograph and CT images, thus showed a "pooping duck" sign [Figure 1c]. The sign results from peculiar appearance of a "duck" made up by carpal bone arrangement and the avulsed fragment resembling a poop ejecting from its rear end. The radiographic impression made by the superimposed carpal scaphoid and lunate forms the beak and body of the "duck" on the volar aspect while the triquetrum forms the rear part of the duck on the dorsal aspect of the wrist. The avulsed triquetral bone fragment, then resembles the loose "poop" ejecting out of the dorsal rear end of the "duck" thus formed, giving the impression of a "pooping duck."

The triquetrum fracture is the second most common carpal injury, after scaphoid fractures, and dorsal cortical fracture is common and managed conservatively with good outcome.[1] Thorough clinical examination should be coupled with CT or magnetic resonance imaging for the comprehensive identification of triquetrum fracture and associated ligamentous injuries.[2] Persistent ulnar-sided pain following the treatment may result from instability, nonunion, arthritis or other adjacent ligamentous injuries. Dorsal cortical fracture with an avulsed fragment lies posterior to the triquetrum and on lateral radiographic images be seen as "pooping duck" sign.[1,3] The fracture fragment resembles "poop" of a duck lying dorsally while the duck shape is formed by scaphoid, lunate, and part of triquetrum body.[3,4]

Declaration of patient consent

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

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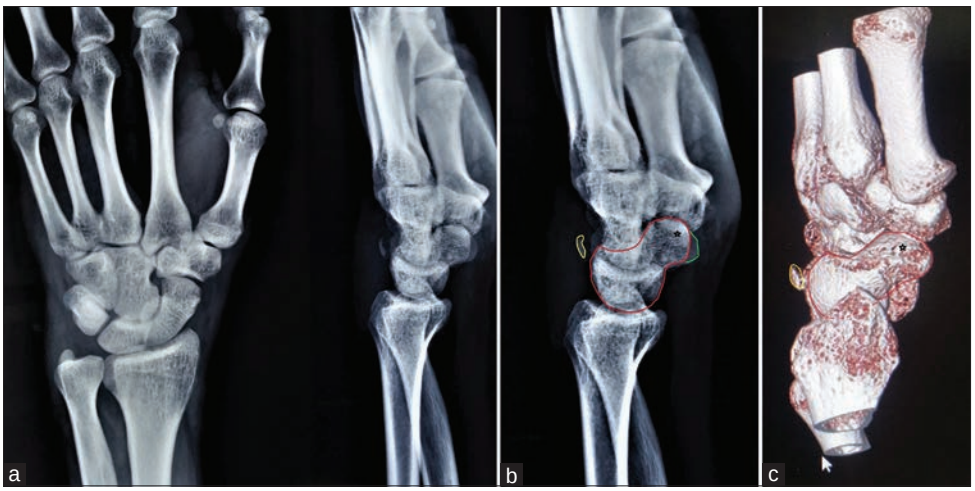

Figure 1: The radiograph of the wrist in orthogonal planes, showing no major fracture except cortical fleck of a bone lying dorsal to the carpal bones in lateral view (a). The impressions on the lateral radiograph (b) with colored lines showing the scaphoid and lunate superimposing on the triquetrum and thus making the body of the "duck" (red line) and the avulsed fragment posterior to it resembles the "poop" (yellow). The CT lateral images corresponding to similar impression as noted in the lateral radiograph (c). CT: Computerized tomography

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Short Communication

Taking a stand against agism: Appeal to the policymakers

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Abstract

Globally, people are living longer with the speed of aging is quite quicker than what was observed in earlier decades. The findings of a recently released report suggest that negative attitudes toward older people are widely prevalent and even have been associated with hazardous impacts on their physical and mental health. The need of the hour is to stop labeling people as elderly and discriminating them or associating some things just due to their age factor. At the same time, there is a great need to address the prevailing negative attitude of health-care professionals toward the elderly. In fact, a global strategy has been formulated and adopted by the member states of the World Health Organization to combat aging successfully by 2030. To conclude, to have more prosperous, equitable, and healthier societies in the future, it is high time to stop categorizing people based on their age and this can happen only when ageist prejudices are eliminated forever.

Keywords: Agism, elderly, World Health Organization

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INTRODUCTION

Globally, people are living longer with the speed of aging is quite quicker than what was observed in earlier decades.[1] Thanks to the development in the health-care industry and other determinants of a healthy life; it has been estimated that the majority of people in the current date are expected to live beyond 60 years of age.[1,2] In fact, it has been projected that by 2050 close to 2 billion people will be aged 60 years and above, which is more than double the estimates in the current year.[1] Further, it has been estimated that four-fifths of the elderly people will be from developing nations by 2050, which in itself is a huge public health concern.[1] Moreover, it has been observed that three-fifths of the participants of a global survey reported that elderly people are not respected in society, with a minimum level of respect in developed nations.[1,2]

AGISM IN TODAY'S WORLD

It is vital to realize that agism can present in various forms and elderly people have been considered often weak, dependent, outdated in terms of technological advancements, and even forced to retire at a specified age without assessing their capacities.[1,2] In addition, it is quite obvious that the health standards of people

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have not improved much in comparison with their increased longevity, and this is predominantly due to the misconceptions and the discriminatory attitude toward the elderly, as a result of which comprehensive policies have not been formulated.[1-3] We must understand that agism has been linked with rising financial expenditure that is required to maintain optimal health.[4] Moreover, the findings of a meta-analysis revealed that the harmful impact of agism on the health status of the older person has been reported across five different continents at both the structural and individual levels in five continents; our systematic review demonstrates the pernicious reach of agism.[5]

NEED OF THE HOUR

At this stage, it is important to understand the challenges which are persisting in society with regard to population aging are multiple, namely, diversified needs, inequity in health, discriminatory attitudes of others toward them, rapidly changing world, etc.[1-3] The findings of a recently released report suggest that negative attitudes toward older people are widely prevalent and even have been associated with hazardous impacts on their physical and mental health.[2,6,7] As a result, they perceive their lives to be of limited value are more prone to depression and other psychological illnesses, and often do not recover promptly from their disabilities when compared with their other counterparts who have a positive attitude toward life.[6,7] Thus, it becomes the need of the hour to ensure that the health and social systems are developed in such a manner to respond effectively to the needs of the anticipated demographic shift.[1,6]

ADDITIONAL CONSIDERATIONS

Moreover, it is quite possible to capitalize on the experience and social and economic contributions, which the elderly people add to society, provided there is a change in their outlook toward them.[2,3] The need of the hour is to stop labeling people as elderly and discriminating them or associating some things just due to their age factor.[5] At the same time, there is a great need to address the prevailing negative attitude of health-care professionals toward the elderly.[2,3,6] In fact, a global strategy has been formulated and adopted by the member states of the World Health Organization to combat aging successfully by 2030.[1]

CONCLUSION

To have more prosperous, equitable, and healthier societies in the future, it is high time to stop categorizing people based on their age and this can happen only when ageist prejudices are eliminated forever.

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Conflicts of interest
There are no conflicts of interest.

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