A diagnostic dilemma: aetiological diagnosis of lymphoedema patients at an Indian multidisciplinary meeting

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Abstract

Lymphatic filariasis (LF) is caused by a mosquito-transmitted infection. The morbidity of this infection can result in chronic, progressive lymphoedema. LF is recognised as one of the most common causes of lymphoedema worldwide with an estimated 40 million people affected. In India, LF is considered endemic with people at risk from across 250 districts. The clinical presentation of LF can have similarities to primary lymphoedema, which is a congenital abnormality of the lymphatic system. Differentiating between the two is challenging, but important for family planning, as well as related phenotypical morbidities. In Kasaragod, India, the Institute of Applied Dermatology (IAD) has developed a unique concept of integrative medicine combining Ayurvedic medicine and yoga with allopathy. The treatment for lymphoedema offered at IAD consists of conservative management with Indian manual lymphatic drainage, compression bandages, yoga, dietitian support, skin soaking and skin oils. During the ninth colloquium, organised by the IAD, an attending team from the UK discussed the application of genetic research, differential diagnosis 'clues' and discussion of research priorities. Correct diagnosis is important to understand and explain inheritance patterns, and to further investigate any other relevant comorbidities. Due to the complexity of these diagnoses, collaboration between these specialist centres across the world is highly valuable.

Lymphoedema is a chronic, progressive condition of accumulation of protein-rich fluid in the interstitial tissue space. Lymphoedema can occur anywhere in the body and does not distinguish in terms of gender, age, socioeconomic background or demographics. The progression of lymphoedema causes irreversible skin and tissue changes, such as fat deposition, fibrosis and papillomatosis. Subsequently, people with lymphoedema will have a lifelong risk for recurrent infection (cellulitis).

Lymphoedema can be separated into secondary and primary. Secondary lymphoedema can be caused by trauma, cancer (and its treatment) and infection, such as lymphatic filariasis (LF). Primary lymphoedema is caused by an error in the development of the lymphatic system, which can present at birth, but may also develop later in life. Different causal gene changes for primary lymphoedema have been identified (Connell et al, 2013). Understanding the genetic cause in primary lymphoedema is important as some of these gene mutations can, in addition to lymphoedema, cause other phenotypical comorbidities, such as ptosis, cleft palate, incompetent veins and/or congenital heart disease in lymphoedema distichiasis syndrome (due to mutations in *FOXC2*). Many are inherited, so there are implications for the patient's siblings and offspring (Connell et al, 2010).

It is well reported that discrepancies in measurement techniques and subsequent reporting, as well as inexplicit lymphoedema definition make it difficult to define the exact incidence and prevalence of primary and secondary lymphoedema (Williams et al, 2005). However, an estimated prevalence report states that over 250 million people worldwide are affected by lymphoedema (Douglass and Kelly-Hope, 2019). The most common cause is LF. It is estimated that 120 million people are affected by LF worldwide with approximately 40 million people affected with debilitating morbidity.

The World Health Organization (WHO) has listed LF among the neglected tropical diseases of the poor. In LF, the damage is caused by infections of the lymphatic vessels with three species of filarial parasites, *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori*. The parasite thrives in lymph vessels and lymph nodes causing obstruction and local damage to the structures (WHO, 2017). This damage to the lymphatic system alone is enough to cause lymphoedema. India harbours one third of the world's LF cases with LF considered endemic in vast geographical areas in 250 districts (Ramaiah et al, 2000).

However, in the Western world, common causes are breast cancer-related lymphoedema and obesity. Twenty per cent of women with breast cancer develop lymphoedema worldwide and this is higher in patients with

gynaecological cancers (DiSipio et al, 2013; Hayes et al, 2017).

As the swelling progresses to adulthood, due to secondary changes in lymphedematous limb and repeated adeno-dermato-lymphangitis (ADLA, equivalent to 'cellulitis'), several subtle clinical features that help to distinguish aetiological causes of lymphoedema at the bed side are masked. ADLA, often due to a bacterial infection, presents with acute high fever, redness, swelling of the affected area and pain. ADLA is triggered by skin breakdown, caused by interdigital fungal infection, eczema, or any local bacterial skin infection. Local skin care and skin hygiene are important to maintain tissue integrity and prevent ADLA.

The progressive nature of lymphoedema can become debilitating, not only causing physical mobility limitations, but negatively affecting psychosocial and emotional functioning (Thomas et al, 2014).

Differentiating between lymphatic filariasis and primary lymphoedema

LF and primary lymphoedema can present in a very similar way. A detailed medical history, including family history, could help in identifying the possible cause for the lymphoedema. In the UK, a family history of lymphoedema is highly indicative of a genetic aetiology. However, in an endemic area for filiariasis, more than one family member may be infected and develop swelling.

Both lymphatic filariasis and primary lymphoedema may present in puberty or adulthood, may be unilateral or bilateral, and involve the lower extremities, including the genital area. Occasionally, the patient can present with other comorbidities, which can make diagnosis more complex. Thorough examination and investigations are essential in identifying the correct diagnosis. This includes examining for varicose veins, birthmarks on the skin, skeletal deformities, congenital heart diseases and asking about abnormalities in bowel movement (clue for possible intestinal lymphangiectasia) and shortness of breath (pleural or pericardial effusions).

Anecdotally, yet to be published data of over 1,500 patients treated at the Institute of Applied Dermatology (IAD) shows that response to conservative treatment in filarial lymphoedema is far more rapid and dramatic in contrast to primary lymphoedema.

Institute of Applied Dermatology, Kasaragod — lymphoedema integrative medicine programme and strategies

The IAD in Kasaragod, India, opened its doors in 1999. Currently in a new purpose built building, it focuses principally on lymphoedema management. This institute uses a novel, integrative medicine concept, combining allopathy, yoga and Ayurvedic medicine, for the best patient outcomes. Additionally, compression therapy using long-stretch bandages and locally available low-cost materials, nutrition, self-management, and health literacy are part of the holistic approach of the clinic undertaken by the multidisciplinary team (MDT).

Patients from all over India travel for treatment at the IAD, with approximately over 700 patients treated a year. During their intense treatment, they stay local to the clinic and attend daily for a period of 2–3 weeks. The costs of the treatment are paid for by the patient themselves, but the IAD provides financial support for 25% of the patients that are in financial need. Each day, patients undergo a range of treatments, including: skin wash and Ayurveda skin tonic phanta soaking, lymphatic massage known as Indian manual lymphatic drainage, treatment for any causes of skin breakdown, which may become bacterial entry lesions, nutritional recommendations, yoga and bandaging (Narahari et al, 2007). By the end of the treatment, the patient and their family are competent in the treatment to enable this to continue on their return home.

Counselling and social support are provided from admission, throughout the initial treatment and on the patients return home (by telephone follow-up) and are an integral part of the care. Follow-up assessments are undertaken 3–4 times a year and additional compression bandages and Ayurvedic skin care oils are posted out from the clinic. In the near future, the IAD is looking at developing an app, in order to be able to monitor patients.

The IAD adopts a rigorous data collection approach to all patients admitted for their lymphoedema treatment. Baseline data consists of lymphatic filariasis specific quality of life questionnaire, gait analysis, episodes of ADLA, environmental factors, such as general living conditions surroundings, accessibly to clean (drinking) water and details on waste disposal. Data are entered on an electronic medical records system using an open-access platform (*www.bahmni.org*) (Narahari et al, 2013; Thomas et al, 2014; Aggithaya et al, 2015).

The IAD conducts national colloquiums on evidence-based integrative medicine and LF. These have been developed as a national platform that provides the opportunity to attend Continuing Medical Education (CME) on bedside clinical evaluations, treatment workshops and training on patient communication skills related to lymphoedema. Medical camps are organised for lymphoedema patients who come from all over India. The IAD invites renowned lymphologists and experts from across the globe on the subject to attend these colloquiums to provide the opportunity for patients to get examined by them in medial camps that are organised as a scientific session.

In 2013–15, the IAD completed discussions on seven future research priorities on lymphoedema through a priority setting workshop involving patients, doctors and scientists (Narahari et al, 2017). The programme was supported by the Indian Department of Health Research. IAD colloquiums have focussed on the road map for implementing programmes to answer these priority research questions. In January 2019, the IAD's ninth colloquium was organised to discuss the sixth priority research question: 'Aetiological diagnosis and Morbidity Management and Disability Prevention of Lymphoedema.'

The IAD Colloquium 2019 invited 104 patients (97 attended) from different geographical and endemic areas of India. The focus of this colloquium was the determination of the exact cause of the lymphoedema and its complexity. The UK team was invited to participate in this colloquium and, in particular, discuss ongoing (genetic) research and the establishment of the network needed for routine diagnostic testing, such as genetic testing and lymphatic imaging. The team from the UK consisted of dermatology consultants, clinical genetics consultant, consultant physician and research nurse practitioners. The India delegation consisted of dermatologists, physicians, medical oncologists, public health experts, vector control officers, yoga experts, Aryuvedic medicine consultants, pathologists, orthopaedicians, basic scientists, statisticians, data scientists, dermatology nurses and lymphoedema therapists.

In addition, a member of the Japanese National Centre for Global Health and Medicine, the President and CEO of the Lymphatic Education, Research Network

and Vice President of Forum for Ethical Review Committees in India and the Principal Secretary to the Ministry of AYUSH, Government of India, participated in the colloquium. Here, the authors present a few of the clinical cases presented at the ninth colloquium. These highlight the variety of patients seen and the difficulties in determining the exact aetiological diagnosis.

Clinical cases

Lymphoedema-distichiasis syndrome

This genetic form of primary lymphoedema may present with lymphoedema of the lower limbs and/or genitalia, in late childhood, puberty or adulthood. This is an inherited, autosomal dominant condition so, in most cases, there is a family history of lymphoedema or varicose veins. However, it may occur *de novo* (i.e. as a new genetic disorder in that individual), so there may be no family history of swelling. The 'handle', or main clue, to the diagnosis is the presence of 'distichiasis'. Distichiasis translates into 'a double row of eyelashes', but in actual fact, these are aberrant eyelashes, arising from the inner eyelid (upper or lower) and are often curved, thus irritating the conjunctiva (*Figure 1*). Careful examination of the inner eyelids may reveal the presence of these aberrant eyelashes — one is enough to make the diagnosis of lymphoedema-distichiasis syndrome (LDS).

The authors looked carefully for these eyelashes in all patients presenting at the IAD ninth colloquium with a phenotype that could point towards LDS — distichiasis was subsequently found in four separate families. Three of them had a family history of lymphoedema — but they were all from endemic areas of filariasis. The severity of the swelling of lymphoedema in these patients was much more apparent than patients seen in the UK, but they responded well to conservative treatment, such as compression, exercise and skin care.

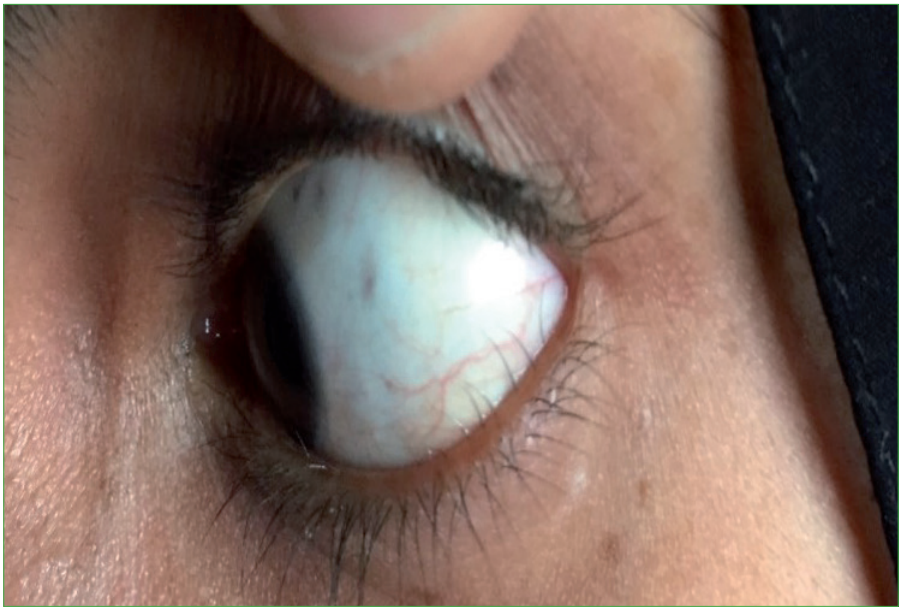

Figure 1. Aberrant eyelashes in lymphoedema distichiasis syndrome.

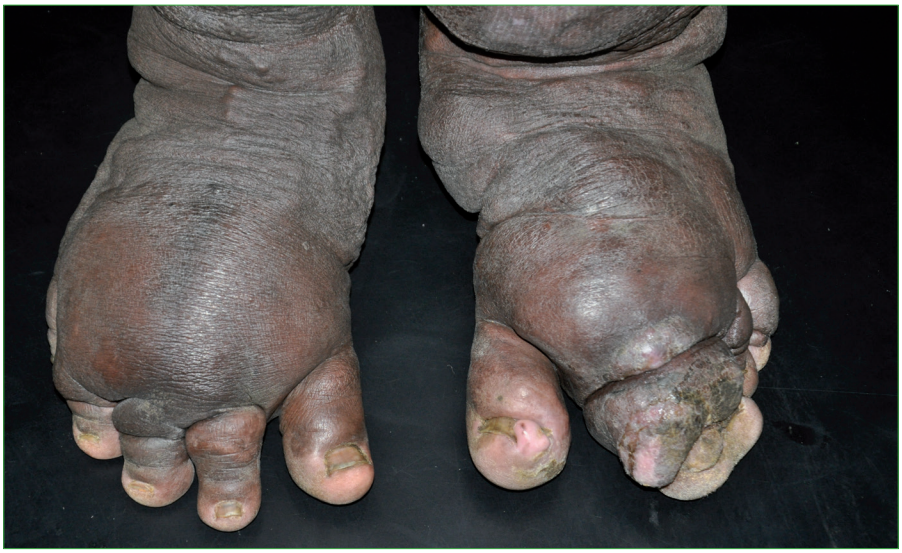

Figure 2. Segmental overgrowth in *PIK3CA* mutation.

Noonan syndrome

A 25-year-old female, presented with swelling of both the lower limbs and genitalia with onset at the age of 8. Further interrogation confirmed that there was leaking of chyle from the lymph blisters in the genital area, especially following ingestion of fatty foods. There was no family history and she was from an filariasis endemic area. Chylous reflux is not commonly seen in LF, but is a rarely recognised complication of LF (Manokaran et al, 2015) and careful examination revealed that she had a mildly webbed neck with low set posteriorly rotated ears and was mildly dysmorphic. There were no other medical problems reported. This pattern of lymphatic abnormality was not typical for LF and her facial features were highly suggestive of Noonan syndrome. This is an autosomal dominant condition, but can often present *de novo*. There is an increased risk of lymphoedema and other lymphatic abnormalities, e.g. pleural effusions. There is a high incidence of congenital heart disease, including cardiomyopathy, atrial septal defect and pulmonary stenosis. An echocardiogram is recommended.

The lymphoedema, particularly swelling of the genital area, and the diagnosis of a 'genetic' disorder, has an enormous impact on this lady's prospect for marriage. The risk of her children inheriting this disorder is 50% and they may be more severely affected.

PIK3CA-related overgrowth disorder

For some patients, the oedema was accompanied by segmental overgrowth and vascular malformations. One man had segmental overgrowth of one leg with limb length discrepancy and vascular malformations, since birth. Although there was some oedema, it was not the predominant problem. The pattern is not consistent with, or caused, by filariasis. These are often caused

by a 'mosaic' mutation (i.e. a mutation in only some cells) in the affected limbs, resulting in the overgrowth. Some of these genes are now known; the most common is *PIK3CA*, a gene that is critical for cell proliferation. Germline mutations in these genes is usually lethal, so although the cause is genetic, the risk to the offspring or siblings is close to 0% (*Figure 2*).

Discussion

Lymphoedema is a chronic progressive condition that can cause physical limitations and psychosocial barriers. It affects children and adults all over the world. Whether the onset of lymphoedema has a secondary or primary cause needs to be understood, in order to adapt possible treatment for the best outcome. In primary lymphoedema in particular, the importance of diagnosis is to prevent complications from other phenotypical features associated with the condition.

Some of the patients seen in Kasaragod with definite primary lymphoedema (e.g. LDS), presented with much more severe swelling that patients with the same condition in the UK. This raises several questions. Do these patients present later because of poor local care and delayed diagnosis? Do they have a dual pathology and are also infected by filariasis? Are individuals with a genetic susceptibility to lymphoedema, more likely to develop LF?

To stop the progression of the lymphoedema, early intervention is important. Testing for infection is complicated; testing for the presence of the three types of microfilaria in the blood can only happen at night as this is the time that the larvae are active. On top of this, the test is not always conclusive (e.g. negative test does not rule out infection). If the adult worms are not laying eggs (microfilaria) anymore, the blood test will be negative. Very remote (and often very poor) areas cannot always be reached, which means there are probably many more LF patients out there.

Genetic testing for the known lymphoedema genes happens in the authors' UK clinics on a regular basis as a diagnostic tool. Genetic testing in India is not offered routinely and not readily available. In addition, it is not only the testing itself, but is the test interpretation and genetic counseling that needs to co-exist accordingly. Genetic testing cannot be offered as a routine test without this network of support.

Knowing the specific genetic cause of the lymphoedema may not alter management but, as some types of primary lymphoedema can be associated with other comorbidities, additional investigations may be required. It is important to look for the genetic fault where possible. Information can be provided to the patient and their family regarding the inheritance pattern of the gene, including the risk of siblings and children also being affected.

UK patients with primary lymphoedema are keen to have a more accurate diagnosis of primary lymphoedema with the specific gene change identified. In the Indian population, the authors were made aware of the implications that a diagnosis related to a genetic cause may have for a person for whom an arranged marriage is planned. Information obtained asked when looking for potential genetic causes of a condition includes family history and whether there are parents who are related to each other (known as consanguineous parents) as this will more commonly result in genetic changes to the children than in unrelated parents. Again, the authors saw patients and families where this was common. The families were also anxious about transmitting this disease to their next generation and inquired if any preventive steps could be undertaken.

The UK team attending the ninth colloquium was inspired by the significant results achieved by the IAD team following the initial intensive treatment period. Seeing patients with large lymphoedematous limbs cross legged on the floor undertaking the yoga class was really impressive. Often in the UK, patients with lymphoedema do not or cannot participate in exercise groups/classes. The positivity of the team, patients and their families and the holistic approach were evident. This mutual positive approach appears to motivate patients and their family members to be significantly involved in their LF management. People with limited resources attended the clinic and continued self-bandaging on their return home, despite the heat and humidity of the Indian climate. Over 70% patients continue their treatment at home and return to the IAD for follow-up assessments (Narahari et al, 2013).

Conclusion

Integrative medicine, combining biomedicine and Ayurveda medicine and yoga, is an effective approach to treat LF. Primary lymphoedema and LF can have similarities, which are complicated to differentiate. However, a correct diagnosis is important, particularly in primary lymphoedema to understand inheritance patterns and assess any phenotypical comorbidities of that gene mutation. International meetings between specialist centres is essential in sharing information, common problems and establishing strong collaborations.

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