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Case Report

Congenital four-limb Lymphedema: A case report

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Abstract Primary lymphedema is a rare genetic, progressive disorder characterized by swelling due to inadequate lymphatic drainage by defective lymphatic vessels. Here we report a case of a teenage girl presenting with primary lymphedema but with erratic family history and features supportive of both a dominant and recessively inherited described mutations.

Key words
Primary lymphedema; PIEZO1-related lymphatic dysplasia; GJC2-related lymphedema.

Introduction

Congenital lymphedema is a rare disorder characterized by progressive swelling of the tissues due to genetic intrinsic defect of the lymphatic vessels, leading to lymphatic dysfunction.[1,2] Here we present a case of a young lady suffering from lymphedema with overlapping clinical features of both dominant and recessively inherited mutations described in literature.

Case report

A 16-year-old girl, born of consanguineous marriage, presented with the complaint of recurrent cellulitis of legs with progressively increasing lymphedema of all 4 limbs which had recently begun to involve her face as well. She was born in a village, at her home, via a spontaneous vaginal delivery. Her mother noticed mild edema of her feet but it did not start progressing and becoming grossly noticeable until she was about 5 years of age. It was bilateral but more on the left side of her body. It gradually progressed, starting from feet, involving both legs, genitalia, both arms for the last one year and now for 6 months, her face as well. She had recurrent episodes of swelling, redness and pain involving one or the other leg, along with fever, for which she had multiple admissions in different hospitals for intravenous antibiotics which settled the episode for some time. For the past one year the episodes had worsened, and she developed constant low grade fever along with night sweats.

Her parents were first cousins and her elder sister who is 22 years of age has no such features but she has had history of pulmonary tuberculosis 4 years back. Her mother gives history of one 2nd trimester miscarriage, one still-birth (cause not known), and another child who died at 3 months due to some respiratory infection (mother reports short history of fever, cough and poor feeding with labored breathing-was not taken to a hospital and he died at home). Her mother did not undergo any antenatal check-up but during our patient's pregnancy, reported no birth complications, and normal developmental milestones. Her mother suffered from small joint arthritis but she chose not to get tested and preferred her local hakeem medications (contents not known but denies the usage of once weekly medication). There is no

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Figure 1 Lymphedema of hands.

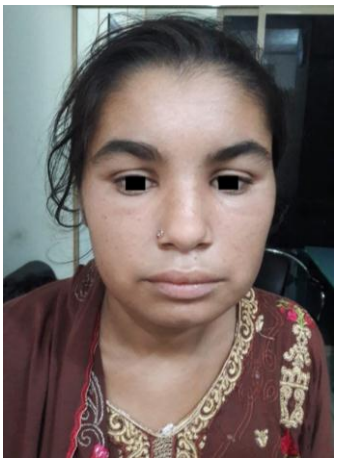

Figure 2 Lymphedema of face, with ptosis.

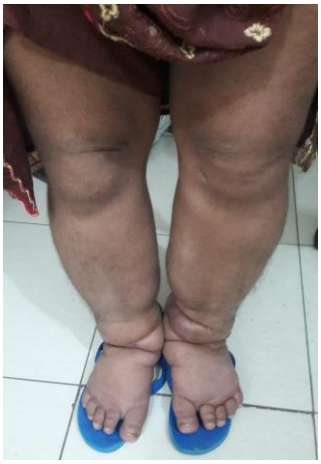

Figure 3 Lymphedema of legs.

family history of similar lymphedema present in any relative. She had menarche at 14 years of age and her menstrual cycle has been irregular till now. She reported no incidence of steatorrhea or frequent diarrhea. She did not attend school due to difficulty in mobility but she does household chores while sitting. On examination, a young lady of normal build and height, with gross lymphedema of both legs, more on the left than on the right, with positive Stemmer sign, and interdigital maceration. Genital lymphedema was also present. On the upper limbs, pitting edema was present, more on the left than on right, especially on the dorsa of both hands. Her face exhibited swelling and puffiness, with broad nasal bridge, increased inter-canthi distance but normal eyelashes. Mild degree of ptosis was also noticed. Her hair was normal with a normal hairline. Her speech and hearing were normal, no microcephaly or any other facial abnormality was noted. She had a sallow complexion with conjunctival pallor. No lymphadenopathy, normal abdominal examination, normal cardiac auscultation, but there was decreased air entry and dullness to percussion on the left lower lung base. She was compliant with the examination and answered the questions readily.

Her labs showed a hemoglobin of 9.9 g/dl, MCV 85 fL, RBC count 3.53* 10^6/UL, HCT 30.1%, MCH 26.3%, TLC 9.6*10^3/uL, Platelets 421 *10^3/uL, ESR 48mm/Hr, with normal LFTs and RFTs. Her abdominal ultrasound revealed a left sided pleural effusion. Pelvic scan showed normal ovaries with developing follicles. Her CT scan showed pleural effusion/ thickening in left lower chest with compressive atelectasis of left lower lung lobe with reduced lung volume, considered likely of tuberculous origin. The effusion could not be tapped. Her thyroid profile was normal. Doppler studies of lower limbs identified incompetent sapheno-femoral junction and massive subcutaneous edema. Doppler study of upper limb revealed normal flow with subcutaneous edema. Lymphoscintigraphy was done of lower limbs. Early dynamic images showed stasis of injection sites bilaterally. Early static images showed minimal visualization of right sided lymph nodes in popliteal and inguinal regions, whereas no nodal uptake in left lower limb noted. In delayed static images, popliteal and inguinal lymph nodes renoted on right side. Faint visualization of popliteal lymph nodes on left side. Final report was bilateral poorly/ minimally visualized lymph nodes consistent with advanced lymphedema. Stool examination was normal and urine complete examination yielded 6-8 pus cell with blood ++. Iron studies could not be done due to affordability issue.

Genetic studies could not be done due to non-availability.

Diagnosis of congenital lymphedema was made.

She was started on anti-tuberculous therapy by the Thoracic Surgery Department and Pulmonology Department on which her fever and night sweats improved. She was prescribed topical antifungals, iron, B12 and folic acid supplementation, as well as given instructions on keeping her legs and arms elevated with compression stockings and physiotherapy. Patient improved on ATT and her ESR decreased on follow up. Her Hb improved to 11g/dl after 3 months. Lymphedema was still the same.

Discussion

Lymphedema is the progressive swelling of tissues due to inadequate drainage of lymph.[1]It can be primary or secondary.[1] Primary lymphedema arises due to the presence of a genetically determined intrinsic defect, leading to aplasia, hypoplasia, malfunction or dysfunction of the lymphatic vessels.[1,2] It is more common in girls than in boys.[3] The secondary lymphedema arises due to extrinsic injury or compression of the lymphatics and/or lymph nodes.[1]

Primary lymphedema is a rare and progressive disorder where the limbs continue to enlarge due to deposition of fibro-adipose tissue. Our patient in the report started developing noticeable lymphedema from the age of 5 onwards, with progressive involvement of all four limbs as well as face. Our initial differential was of Hennekam syndrome[7] which is characterized by systemic lymphatic malformations, facial dysmorphia and mental retardation. She did not have any cognitive dysfunction, but some of her facial features supported the diagnosis of *PIEZO1*-related lymphatic hydrops/generalized lymphatic dysplasia, another type of generalized lymphatic malformation. This is an autosomal recessive condition due to mutation in *PIEZO1 gene*.[4] *PIEZO1* is a mechanically activated calcium permeable ion channel, which plays an essential role in fetal blood and lymphatic vasculature development at 17th week of gestation.[5] It is characterized by widespread lymphedema with systemic involvement such as pleural effusion, chylothoraces and may present with non-immune hydrops.[6] In contrast to Hennekam syndrome, the intelligence is normal, there are no dental anomalies and also there is no evidence of renal or intestinal lymphangiectasias as yet.[4,7] Our patient did not reveal any systemic involvement on her CT scan apart from left lower pleural thickening which could not be completely attributed to it. Her mother had several miscarriages for which she did not get any medical help so without any genetic screen, this condition cannot be completely ruled out. Our patient still requires long term follow-up so that if any systemic involvement does start to develop it can be screened early on.

Another subtype which fits our patient's profile is *GJC2*-related lymphedema, an autosomal dominant late-onset four limb lymphedema.[4,8] It is caused by a missense mutation in *GJC2* which alters gap junction function and subsequently lead to disruption in lymphatic flow.[8] It is associated with varicose veins and our patient showed incompetent sapheno-femoral junction. Our patient also had mild degree of ptosis. The *GJC2*-related lymphedema is autosomal dominant but in our patient's case, there was no family history apart from unexplained miscarriages of her mother.

Our patient had undergone menarche and pelvic sonogram did not reveal any abnormality so Turner's syndrome was ruled out.[9] Her eyelashes were normal so Lymphedema-

Distichiasis was also ruled out clinically.[9] Another differential could possibly be Emberger syndrome, [4] which is characterized by childhood onset of lymphedema along with a predisposition to development of myelodysplasia and acute myeloid leukemia.[10] It is autosomal dominant which was not the case with our patient. Alterations in *GATA-2 gene* are responsible for it. Our patient still needs regular monitoring and follow up to rule out this syndrome as well in absence of genetic testing.

Conclusion

Even though it has been nearly 400 years since the lymphatic system was described, it has remained a poorly understood subject. Without the genetic analysis no confirm diagnosis can be made in her case which highlights the need of developing the genetic testing in Pakistan at subsidized rate by the Government as consanguinity and subsequently genetic disorders are rather common in our society. Our patient was subsequently counselled regarding the nature of her disease and the management to be done including manual lymphatic drainage, management of recurrent cellulitis as well as psychological support for psychosocial morbidity.[11]

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