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Case Report

Propranolol Alleviating the Challenging Clinical Course of Birth Onset Generalized Lymphangiomatosis. A Case Report

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ABSTRACT

Background: Cystic hygromas, interchangeably named Lymphangiomas, are rare, congenital, benign lesions due to an abnormal lymphatic system development that tend to occur mostly in the head, neck, and oral cavity

Case Presentation: This is a case of 18 year old male patient Syrian, smoker, with a history of multiple cystic hygromas since birth along with a generous surgical history of multiple laparotomies for intrabadominal cystic excisions, splenectomy herniorrhaphies (bilateral inguinal hernias and 2 incisional hernias due to laparotomies) left orchieopexy then testiculectomy, scrotal skin graft , multiple abdominal radioguided cystic drainage and sclerotherapy; presented to our care center for fever, dry cough, pleuretic chest pain, and mild abdominal pain with watery diarrhea.

Conclusion: Cystic Hygroma is still being considered as a rare entity and can virtually occur in the whole body sites mostly at head and neck regions as explained above. Challenges in this disease is by finding cases where the presence of such cystic lesions is in extremely rare and unusual sites as well as different treatment modalities and prognostics depending on the site and size of the detected cystic formations.

Introduction

Lymphangiomas are rare congenital benign tumorsdue toabnormal lymphatic development. In most cases, they are idiopathic but can accompany other genetic disorders such as Turner, Down and Noonan syndromes [1].Rarely, these malformations can be acquired due to trauma or inflammation [2, 3]. Histologically, lymphangiomas are classified as: Lymphangioma circumscriptum or capillary lymphangioma (capillary sized lymphatics) that is superficial and the other two deep ones the cavernous lymphangioma (larger actively growing lymphatics) and the cystic lymphangioma interchangeably named cystic hygroma (macroscopic cystic lymphatic spaces with collagen and smooth muscle content) [4-6]. The lymphatic proliferation can be microcystic (< 2 cm), macrocystic or cystic hygromas (> 2 cm), or mixedaccording to the lymphatic cavity sizes. It is due to failure of communication between lymphatic and venous systems, where dilation of these congested lymphatics occurs yielding to cystic lesions that contain milky, serous, serosanguinous or straw-colored fluid [7]. Lymphangiomas account for 5.6% of all benign tumors in infancy and adulthood [8]. Cystic hygromas are mainly present perinatally (60%) or at age of 2 years (90%) and mostly invade head and neck region (40-70%) extending into mediastinum in 10 % of cases[7, 9].

Generalized Lymphangiomatosis (GL) and more recently Generalized Lymphatic Anomaly (GLA) is used when lymphangiomas involve multiple organs frequently the bones, spleen, liver, mediastinum, lungs, pleura and neck or any other site except the brain which lacks lymphatics. When the disease is confined to the pulmonary lymphatics,

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it leads to the rare syndrome of Diffuse Pulmonary Lymphangiomatosis (DPL) [10, 11]. we report a case of widespread lymphangiomatosis who suffered since late infancy from extensive surgical and invasive radiological interventions and their complications until he was started on medical treatment with propranolol at our medical institution which changed dramatically his quality of life over the last 7 months.

Case Report

An 18-year-old Syrian refugee in Lebanon since 2013, presented on July 24, 2018 with fever, abdominal pain and watery diarrhea of one-week duration. He reported dry cough, pleuritic chest pain and progressive dyspnea over several weeks and weight loss of 7 kg over the last year. His medical history was significant for chronic hepatitis C and birth onset diffuse lymphangiomas resulting in a generous surgical history starting at age of one year of multiple laparotomies for intraabdominal cystic hygromas excisions, herniorrhaphies (bilateral inguinal hernias and 2 incisional hernias due to laparotomies), excision of right scrotal hemorrhagic lymphangiomas with right orchiopexy then orchiectomy and scrotal skin graft at age of 11, and splenectomy at age of 17 for profound thrombocytopenia related recurrent bleedings (Figure 1A). Since 2015, he underwent multiple radio-guided abdominal cystic drainages and sclerotherapy with alcohol and Glubran by a Lebanese invasive radiologist with the last radio-intervention aborted 6 weeks prior to presentation. Patient has also received multiple courses of antibiotics for recurrent infected collections.

Figure 1A: Image showing the multiple laparotomy midline incision sites (yellow arrows), Splenectomy incision (black arrow), scrotal chylous fluid oozing point (red arrow) and right thigh donor site for scrotal skin graft (green arrow)

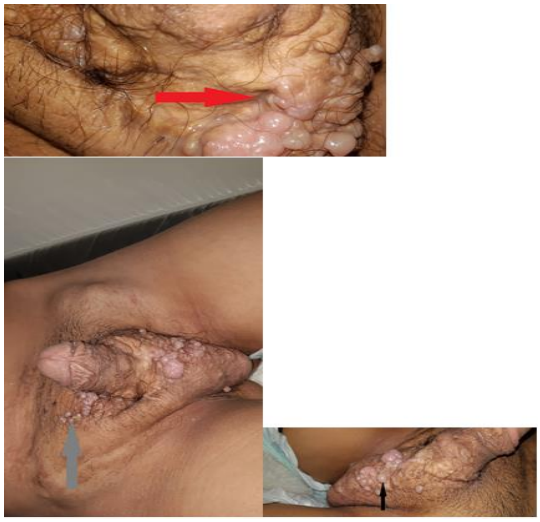

Figure 1B: Skin fleshy Cystic lesions on inguinal (gray arrow) and scrotal areas (black arrow) and chylous oozing site on scrotal area (red arrow)

On physical exam, patient had BMI of 17. His abdomen was distended. He had multiple flesh like scrotal and inguinal vesicles some showing verrucous changes consistent with lymphangiomas circumscriptum draining foul smelling serosanguinous and milky fluid through tiny openings connected also to the abdominal cysts (Figure 1B). Patient was wearing diaper requiring many changes per day due to copious drainage. Imaging studies showed mild right-side and moderate to severe left-side pleural effusions (Figure 2A and D). CT scan abdomen-pelvis showed large amount of loculated fluid collections in the intraperitoneal and retroperitoneal cavity (Figure 2B, C and D). An inter muscular collection is seen in the right abdominal wall, with diffuse abdominal wall edema/ fluid collections extending down to the inguinal areas bilaterally; the liver shows multiple tiny low-density lesions in all segments, suggestive of liver lymphangiomas (Figure 2E, F and G), Multiple bony lytic lesions in spine and pelvis bone (Figure 2H).

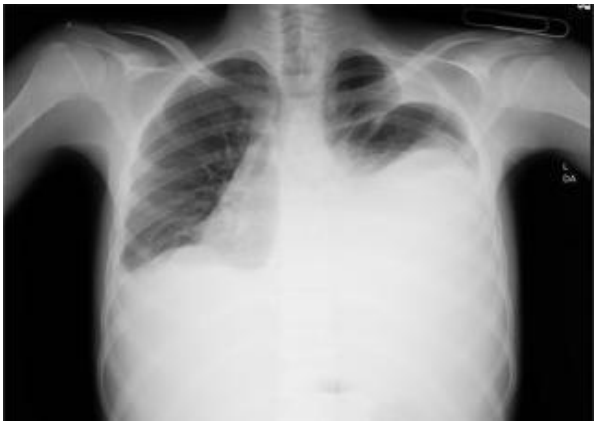

Figure 2A: Chest X ray showing mild right and moderate-severe left pleural effusions.

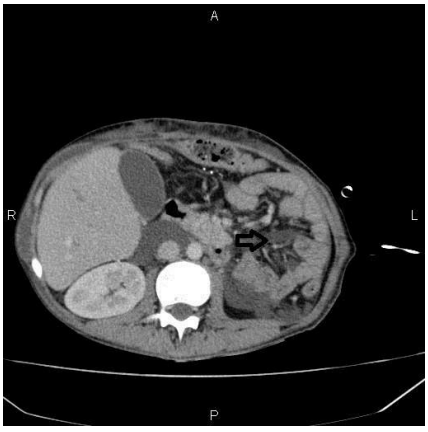

Figure 2B: Intraperitoneal (mesenteric) cystic collection (Black Arrow).

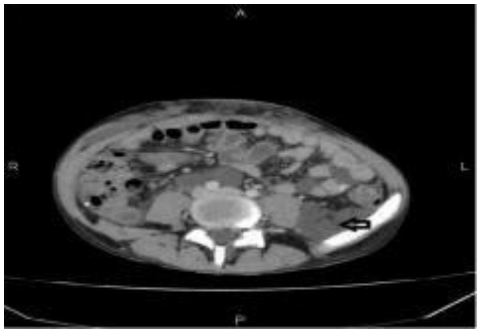

Figure 2C: Retroperitoneal cystic collections.

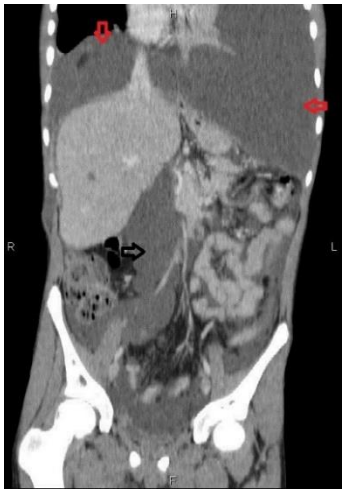

Figure 2D: Reconstructed Coronal images of abomen and pelvic CT scan showing loculated cystic lesions along the mesentery (Black arrow) and bilateral pleural effusion (Red arrow).

Labs showed WBC 22.8 10^9, Neutrophils 89.1%, lymphocytes 5.8%, Platelets 1189.10^9. CRP 183. Cholesterol 97mg/dl (low) TG 113mg/dl, HDL 29mg/dL, LDL cholesterol 45mg/dL; total protein: 45.2 g/l, albumin 16.7 g/L (low), globulin 29 g/L (NL); LDH 800, Alkaline phosphatase 215, Gamma-GT 183, ALAT 69; Bilirubin, PT and PTT were normal. A left side pleural tap drained 1 L transudative chyle with RBC 3400/ microL, WBC 370 /microL, Neutrophils 59 %, lymph 27%, mono 11%, Eosinophils 3%, Glucose 114, protein 14.7 g/L, LDH 156 IU/L, TG 1547 mg/dl (high), amylase 47 u/L; CYTOLOGY showed reactive pleural fluid, negative for inflammation, free of atypical cells. Patient was admitted under care of the Infectious diseases team and started empirically on treatment for C.difficile colitis and infected abdominal and scrotal collections which grew later E coli ESBL.

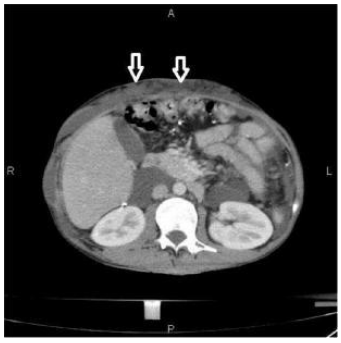

Figure 2E: Anterior abdominal wall intermuscular collections (white arrows).

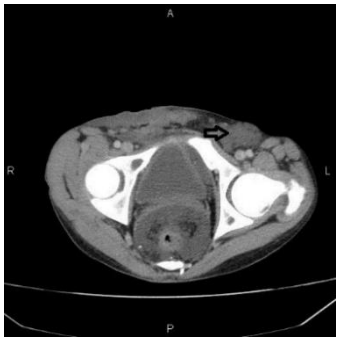

Figure 2F. Inguinal Area cystic fluid (black arrow).

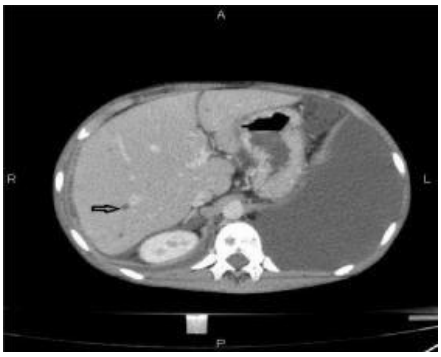

Figure 2G: Liver cystic Lesions (black Arrow).

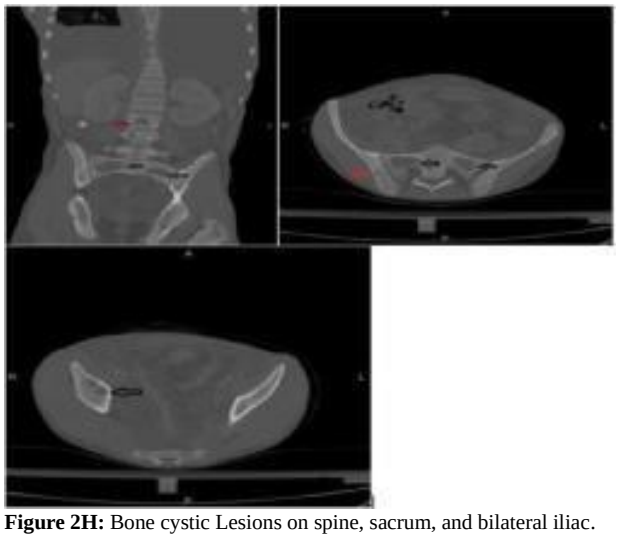

Figure 2H: Bone cystic Lesions on spine, sacrum, and bilateral iliac.

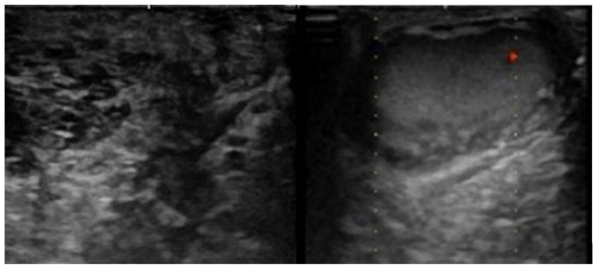

Figure 2I: Ultrasound testicles showing cystic lesions in scrotal wall and a normal testis.

Ultrasound of testis showed absent right testis, normal left testis, scrotal cysts, subcutaneous thickening of scrotal regions (Figure 2I). Further work-up was not approved by the insurance for refugees. By d 6 of admission, fever and diarrhea resolved. On d 11, he was discharged on antibiotics, aspirin and high protein diet. Medium-chain triglyceride diet couldn't be offered due to financial reason. He was scheduled return to the cardiovascular outpatient clinic to plan for left side decortication. On September 6th, he was readmitted to the surgical department and underwent left pleurectomy after double lumen intubation, left thoracotomy at sixth intercostal space, suction of 3 L of odorless chylous fluid, 2 LN taken for pathology, 2 chest tubes anterior and posterior inserted. Then put under wall suction -100 mmh2O and incentive spirometer.

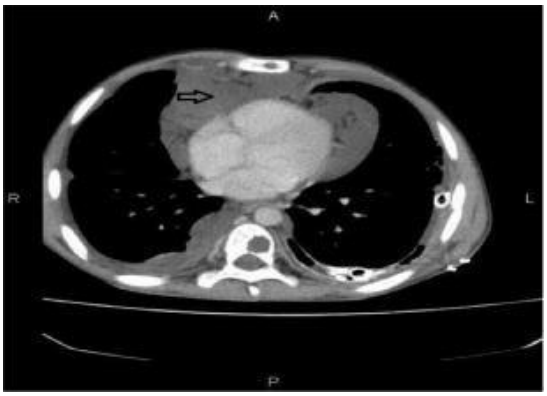

Figure 2J: Mediastinal Cystic collections (Black Arrow) with left chest anterior and posterior chest tubes seen post decortication

Surgical pathology report

1. Pleura of left lung: acute suppurative pleuritis compatible with bacterial infection, no signs of specific infection and no neoplasia seen.
2. Ganglion of left lung, slightly enlarged lymph nodes showing mild follicular hyperplasia, negative for inflammation or neoplasia

Pleural fluid cx was negative. He started draining 1500 cc of chylous fluid / 24 hrs. in both chest tube bottles. At d10 post-op, drain reached 8 L chyle per day, patient was still hemodynamically stable and started on IV albumin. On the next day, a bedside pleurodesis was done using both chest tubes by slurry talc mixed with povidone-Iodine then with talc alone 2 days later. On d 14 post-op, Bipap started to help in pleurodesis and to maintain good lung expansion. Follow-up CT scan showed significant decrease in the left pleural effusion. The lungs show septal thickening and mild vascular congestion. Multiple collections are noted in the superior, anterior and mid mediastinum without extension from or to the neck, showing a fluid density (4HU) compatible with multiple hygromas (Figure 2. I). Chest tubes removed d 25 post-op after reaching 180cc total daily drainage and having normally expanded lung on x-ray with mild left side pneumothorax.

Patient was discharged after one month of hospital stay during which he was maintained on antibiotics for his suppurative pleuritis as well as re-infected groin and scrotal collections. Two weeks later, he presented to the ER with high grade fever. WBC was 33 10^9. CT chest showed huge complicated left pleural effusion with calcification in keeping with the patient history of pleurodesis, the effusion is probably occupying 80 to 90% with complete collapse of left lung. Pleural tap aspirated turbid bloody exudative fluid consistent with the recent surgery, triglyceride was only 51 mg/dl. culture didn't grow any germ. On the second day, 600 ml of turbid fluid were drained upon the insertion of a chest tube. Patient was started on Bipap to help relief the trapped lung. Given his intractable left chylothorax despite the recent surgical intervention, medical treatment options were discussed with the hemato/oncology team and patient was started on d12 of hospitalization on propranolol, a cheap and available drug, 0.5 mg /kg to be increased progressively to 2 mg /kg as needed and tolerated. Also, a request was sent to a humanitarian organization to sponsor Bevazicumaban alternative treatment for his generalized lymphangiomatosis which might also decrease his thrombocytosis. On d19, the left lung was completely expanded and chest tube was removed with 150 cc /24hrs. Patient was discharged on the next day on, amoxiclav and ciprofloxacin to complete 6 weeks of antibiotic therapy, aspirin and propranolol 0.5 mg /kg.

Three weeks later, he was readmitted again for fever and leukocytosis. Ct scan chest showed recurrence of left chest fluid collection with subsequent collapse of the underlying lung parenchyma. Chest tube was inserted, pleural fluid analysis showed Infected pleural fluid with streptococcus imitis growing in blood bottle. Patient was treated for his empyema, his propranolol dose increased to 1 mg/kg (total 50 mg). He became afebrile on day 2 of admission, and chest tube removed on day 8. On day 10 he was discharged on amoxiclav to complete his course for empyema, propranolol 50 mg per day and aspirin. Patient had subsequent follow-ups in the infectious diseases and cardiovascular clinics. He clinical condition improved markedly: He gained 6 kg over 4 months. On May 21th, Follow-up chest x ray didn't show any new collection since last chest tube was removed. Six months from propranolol 1 mg /kg, physical exam showed non distended abdomen, smaller scrotal and groin cutaneous lymphangiomatosis with chylousdrainage reported to be 5 times less than before as per the number of diaper changes.

Discussion

Generalized lymphangiomatosis, an extremely rare and non-curable disease, can be devastating when it affects multiplevital organs and leads to many complications. Diagnosis is made early if clinical presentation is suggestive including low attenuation cystic lesions involving different body sites with bone involvement which occurs in > 75% [12]. However, it might be delayed necessitating extensive investigations with sometimes fatal outcome when presenting symptoms are non-specific like in pulmonary involvement [13, 14]. Symptoms depend on the size of the tumor, the location and the extent of involvement. Macrocystic lesions cause compression of major structures leading to hoarseness (larynx), dyspnea (trachea), and dysphagia (esophagus) [15-17]. For intraabdominal hygromas, symptoms are nonspecific including dull pain, Nausea/Vomiting, constipation, diarrhea, abdominal distention, fever and ascites or related to the complications like volvulus [18]. Thoracic involvement present with cough dyspnea chest pain and wheezes due to lung infiltrates, chylothorax or chylopericadium. Spleen involvement can lead to hemorrhage or portal hypertension. Pain and pathologic fractures are associated with bone lesions. Sometimes patient may present with infected, hemorrhagic and ruptured lymphangiomas.

Imaging recommendations for diagnosis are Ultrasound, Magnetic resonance imaging (MRI) and Ct scan. MRI is an accurate and safe modality to study lymphatic circulation with minimal invasiveness and absence of radiation. Cystic lesions appear as non-enhancing thin-walled multiloculated masses with near-water attenuation [19]. Lymphangiography and lymphoscintigraphy can be also used with the latter being minimally invasive and not known to have any side-effects but lymphangiography provides more detailed images [20]. In case of pulmonary lymphangiomatosis open biopsy is more diagnostic than transbronchial biopsy [21, 22]. Treatment of GLA is mainly palliative guided by the symptoms, anatomic location and complications. Due to the rarity of the disease no clinical trial has been carried and there are no treatment guidelines. Currently, the surgical excision is the treatment of

choice for localized lymphangiomas with tendency for the lesions to recur in 20% of cases even after apparent complete surgical excision [23]. Sometimes, excision is done partially due to the relation to surrounding structures. Parietal pleurectomy, pleurodesis and ligation of the thoracic duct are indicated to reduce recurrent pleural effusion [24, 25]. Spleen involvement with consumptive coagulopathy bleeding, hypersplenism and portal hypertensioncan lead to splenectomy. Separate cases of liver transplant, lung transplant and scrotal excision with full thickening graft have been reported [26-28]. Other treatment modalities include sclerotherapy with alcohol, bleomycin, OK-432 and doxycycline [29-34]. Laser and radiofrequency are also being used for cystic lymphangiomas.

Percutaneous aspiration can be performed on temporary basis to reduce the size of a compressing cystic hygroma but should be avoided due to high risk of infection, bleeding and recurrence. Systemic therapy has included cyclophosphamide and interferon alpha both with considerable side effects [35-37]. More recently, treatment with propranolol, sirolimus and bevacizumab have been shown to decrease recurrent pleural effusions and lymphatic proliferation. Propranolol, a nonselective β-blocker, works by reducing the levels of Vascular Endothelial Growth factor (VEGF)which influences lymphatics proliferation [38]. When used at 0.5 mg/kg body weight and increased to 4 mg/kg per day, it induced progressive decrease in pleural effusion in a 13-year-old girl [39]. Sirolimus, an immunosuppressant used in renal transplant, is a mammalian target of the rapamycin Inhibitor (mTOR) which is overexpressed incutaneous vascular malformations and ananti-angiogenic factor impairing the production of the VEGF which was proved to be effective in diffuse lymphangiomatosis [40-42]. Bevacizumab, a monoclonal antibody that binds to the (VEGF) type -A, was successfully used in cases of GLA and DPL [43, 44].

Conclusion

Generalized lymphangiomatosis is still being considered a rare disease which can virtually affect the whole body. Intractable complications can issue leading to therapeutic challenge where both surgical and sclerosing therapy can fail. Propranolol a cheap and easy to access drug with few side effects, can be used early following the diagnosis which may delay the progression of the disease and avoid unnecessary multiple interventions and organs loss like in our case.

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Ethical approval and consent to participate

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Consent for publication

A consent was obtained for publication.

Conflicts of interest

None.

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