Generalized lymphatic anomaly: an unusual cause of mediastinal widening - A case report
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Abstract
While simple lymphatic malformations which may be microcystic or macrocystic (Cystic hygroma) are quite common, complex lymphatic anomalies such as generalized lymphatic anomaly are uncommon. Due to its rarity and nonspecific presentation, diagnosis may often be delayed. A 7 yr old male presented with non-specific respiratory symptoms and knee pain. Chest imaging findings of low attenuation soft tissue mass with infiltration along the lymphatic distribution adjacent to the bronchovascular bundles and multiple punched out lytic lesions in the bones with preserved cortex were seen. In the given clinical scenario, laboratory findings, these imaging findings were highly suggestive for generalised lymphatic anomaly. We suggest a complete radiological evaluation in such children as imaging can be highly suggestive even in the absence of genetic or histopathological diagnosis.

Keywords: Generalised lymphatic anomaly; Kaposiform lymphangiomatosis; central conducting anomaly; Gorham stout disease; lymphatic anomalies

Introduction
Simple lymphatic malformations such as microcystic and macrocystic lymphatic malformations are commonly seen, while complex lymphatic anomalies which include Generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis (KLA), Gorham stout disease (GSD) and central conducting lymphatic anomaly (CCLA) are rare disorders. Generalized lymphatic anomaly (GLA) is a rare complex lymphatic anomaly characterized by abnormal proliferation of lymphatic vessels. Exact incidence of GLA remains unknown owing to its rarity. It is has a multiorgan involvement yet thoracic involvement is uncommon. Thoracic involvement in GLA may have a poorer prognosis when compared to other sites of involvement. Skeletal involvement have typical imaging features which can help in distinguishing it from other complex lymphatic anomalies such as Gorham stout disease. Management of this entity is largely supportive.

Case Presentation
A 7 year old male child presented to the outpatient department with complaints of dry cough and breathlessness on and off since one and half years with increase in severity from last 6 weeks. There was no history of fever or wheeze or significant loss in weight. The child also had been complaining of knee pain for past 6 months. The birth history was unremarkable. There was no family history of asthma or tuberculosis. On general physical examination the child appeared weak and emaciated with lower BMI for his age. The child had stable vitals with mild pallor, no icterus or cyanosis. There were no palpable...
lymph nodes. Chest examination revealed normal air entry bilaterally with few bibasilar crackles. No organomegaly or palpable mass was noted on abdominal examination. Neurological examination was also unremarkable. Complete blood count revealed a hemoglobin of 10mg/dl and a platelet count of 141000/µL suggestive of mild anemia and thrombocytopenia. Total leucocyte and differential leucocyte counts were normal.

In view of the clinical complaints of cough and breathlessness and knee pain, an X ray chest and AP radiograph of the knee was requested. The frontal radiograph revealed a well-defined soft tissue density lesion causing symmetric mediastinal widening from the level of thoracic inlet to the level of diaphragm. The trachea was central with no displacement or luminal narrowing. The lesion was seen to silhouette the right and left cardiac borders and the descending thoracic aorta. Hilar vessels were seen through the lesion suggesting the possibility of a multi-compartmental mediastinal mass. Few reticulo nodular opacities were also noted in both lung fields, more prominent in bilateral lower zones. No pleural or pericardial effusion was seen. Few small well defined lytic lesions having a punched out appearance were also noted involving multiple ribs, right scapula and metaphysis and diaphysis of left humerus.[Fig.1a] On AP radiograph of knee, multiple punched out lytic lesions were observed in bilateral distal femoral metaphysis and proximal metaphysis of bilateral fibula and left tibia.[Fig.1b]

In view of the above findings, a contrast enhanced CT of the chest was done to know the nature and extent of the anticipated mediastinal mass and lung findings. Contrast enhanced CT chest revealed a large homogenous low attenuation, poorly enhancing multicompartmental mediastinal lesion spanning from anterior to the posterior chest wall. The lesion showed no evidence of calcification or fat within. The major aortic vessels and its branches were seen to course through the lesion without any luminal attenuation or obliteration. This soft tissue lesion was also seen to extend along the bronchovascular bundles. Lung window revealed bilateral septal thickening in peribronchovascular distribution reaching up till the pleural surface with sub pleural nodules. No pleural effusion or pericardial effusion was noted. Cardiac size and morphology appeared normal. Visualised sections of liver and spleen showed no focal lesions, minimal extension.

**FIG1:** Frontal radiograph in the child demonstrating soft tissue density lesion occupying the mediastinum from thoracic inlet to the diaphragm silhouetting bilateral cardiac borders, descending thoracic aorta suggesting a multicompartmental lesion. Multiple punched out lytic lesions are noted in ribs(curved white arrows), right scapula (notched white arrow) and humerus(straight white arrows).

**FIG 1 (b):** AP radiograph of bilateral knee shows multiple small punched out lytic lesions in bilateral distal femoral metaphysis and proximal metaphysis of bilateral fibula and left tibia with preserved cortical outline.(straight white arrows).No associated soft tissue lesion is seen.

**FIG2:** Contrast enhanced CT axial (a) and coronal reformatted image(b) shows a low attenuation poorly enhancing multicompartmental soft tissue density lesion (star) insinuating between the vessels of mediastinum without any luminal narrowing or obliteration. It can be seen infiltrating along bronchovascular bundles bilaterally.(white arrows)Axial bone window(c) demonstrates multiple lytic lesions in right scapula and vertebral body. Axial lung window image (d) reveals nodular septal thickening along peribronchovascular distribution reaching up till pleural surface(notched black arrows) with sub pleural nodules.(straight black arrows) Axial soft tissue window(e,f) depicts no focal lesions in liver or spleen with minimal periaortic soft tissue(curved white arrows).

of soft tissue was also noted along the visualized upper retroperitoneum surrounding the aorta. [Fig.2] An ultrasound of the abdomen and neck was unremarkable. In view of the long clinical course and imaging morphology of chest and musculoskeletal lesions an imaging diagnosis of generalized lymphatic anomaly /kaposiform lymphangiomatosis was considered. Parents of the child had refused genetic testing or histopathological examination. However, absence of any hemorrhagic effusions or any clinical history of hemoptyis/bleeding, minimal decrease in platelet count and a less aggressive clinical picture favored a diagnosis of GLA.

Discussion

Complex lymphatic anomalies are rare conditions which occur due to anomalous embryogenesis of the lymphatic system. [1]These include Generalized lymphatic anomaly (GLA), kaposiform lymphangiomatosis( KLA), Gorham stout disease (GSD) and central conducting lymphatic anomaly (CCLA). These are associated with significant morbidity and mortality. [2]Overlapping clinical symptoms and imaging appearances are often seen amongst these which pose a diagnostic difficulty. Generalised lymphatic anomaly is usually seen in childhood though may be diagnosed in adults and has no gender predilection. Exact incidence of GLA remains unknown owing to its rarity. The imaging features are mainly based on case reports due to relative rarity of this disease. However, imaging can be suggestive of diagnosis as biopsy may not always be possible in these cases.

The presentation is variable and the clinical course varies according to site of involvement and extent of disease. Different sites involved includes the thorax, liver, spleen, retroperitoneum and the skeletal system. Thoracic involvement has been linked to a poorer prognosis when compared to other organ involvement. [3]

The thoracic manifestations of GLA seen on imaging include a soft tissue thickening/low attenuation soft tissue mediastinal mass. Peribronchovascular septal thickening, diffuse or segmental having a variable extension to subpleural surface has also been reported. Pleural effusion of variable nature is another observed finding. Osseous involvement in GLA is seen to favor the appendicular skeleton with multiple sites involved in a non-contiguous manner. These have been described as non-contiguous punched out lytic lesions without sclerotic rim with preservation of cortex, features which were seen in our case.

Abdominal involvement may manifest as cysts within the viscera such as pancreas, spleen, liver or kidney with or without associated organomegaly. These may well be demonstrated on sonography. Our case however did not reveal any abdominal imaging manifestations.

These imaging findings of GLA are often indistinguishable from KLA and distinction is based on a more aggressive clinical picture of hemoptyis, hemorrhagic effusions, thrombocytopenia and high mortality seen in KLA. KLA is considered to be a more aggressive disease presenting early in childhood and thought to be arising from GLA. Thoracic involvement is much more common in KLA in comparison to GLA. In patients with hypofibrinogenaemia, significant thrombocytopenia, hemoptyis and hemorrhagic effusions, KLA should be suspected over GLA. Diagnosis may be inferred clinically if biopsy is unsafe. Recent studies are investigating the role of genetics in these anomalies and it was found that somatic NRAS p.Q61R variant has a role in pathogenesis of KLA.[4] Though the genetic testing and histopathology was not done in our case, mild clinical course with no pleural /pericardial involvement and non-significant thrombocytopenia suggested the possibility of GLA over KLA.

Another complex lymphatic anomaly associated with osseous and soft tissue involvement is Gorham stout disease. Clinical presentation is often with pain and bone fractures. The osseous lesions in GSD are characterised by progressive osteolysis and cortical destruction (also called as “vanishing bone disease”) and peri osseous infiltrating soft tissue in contrast to GLA where the cortex is preserved and there is no periostial soft tissue.[5] The lesions can be appreciated well, both on plain radiography or CT. Greater number of bones are involved in GLA when compared to GSD. Appendicular skeleton involvement is also more commonly observed with GLA (A comparative study between GLA and GSD has reported that ribs are most frequently involved in both the diseases. However, skull, clavicle, and cervical spine are more commonly involved in GSD whereas thoracic spine, humerus and femur are more commonly involved in GLA). [6]Punched out lytic lesions were observed in our case with involvement of scapula, ribs, thoracic vertebrae, humerus, femur, tibia and fibula with extension to the cortex, however there was no cortical resorption. Biopsy from the rib lesions for diagnosis is discouraged because of the risk of development of refractory pleural effusions post biopsy. Recently, imaging findings have been considered to differentiate between GLA and GSD.[3,6]

Central conducting lymphatic anomaly (CCLA) is another complex anomaly wherein imaging manifestations are poorly described owing to its rarity. It results due to failure to drain the lymph into venous system due to abnormality of central channels like thoracic duct or cisterna chyli. Depending on the site of the anomaly, manifestations such as chylothorax, pulmonary lymphangietasias, chylous ascites, protein-losing enteropathy, cutaneous vesicles, or superficial chylous leaks may be seen.[1] Osseous changes can also be seen in this entity as focal areas of hyperlucency due to dilated intraosseous channels or a permeative appearance. Ectatic lymphatics along the course of central lymphatics seen on MRI should raise the suspicion of this anomaly which is confirmed by lymphangiography.

Treatment in complex lymphatic anomalies is based on management of symptoms and controlling the growth of abnormal lymph vessels. Treatment options may include surgical procedures to drain excess fluid, medications to help control bleeding, and chemotherapy to help stabilize the condition. Current therapy is supportive with sirolimus as single agent or in combination with bisphosphonates. [7] Sirolimus is an mTOR inhibitor which can prevent lymphangiogenesis and decrease lymphatic endothelial cell activity. [8]

Conclusion

GLA is a complex lymphatic anomaly having multiorgan involvement. The presence of characteristic osseous lesions along with blood parameters may help to distinguish these from other complex lymphatic anomalies such as KLA, GSD and CCLA. Histopathology is important for diagnosis however often it is not feasible due to patient refusal of invasive procedure or the risks of refractory effusions. In such settings the characteristic imaging appearances in the correct clinical scenario can be highly suggestive of this entity.

List of abbreviations

GLA: Generalized lymphatic anomaly; KLA: Kaposiform lymphangiomatosis; GSD: Gorham-Stout disease; CCLA: central conducting lymphatic anomaly; CT: Computed tomography; MRI: Magnetic resonance imaging; mTOR: Mammalian target of rapamycin

References