

Case report

Recurrent pneumothorax, skin lesions and frequent urination

A 25-year-old male is admitted with complaints of dry cough for the past 5 years, and increased thirst, urinary frequency and output for the past 18 months. He also complains of shortness of breath on climbing a flight of stairs, and itchy lesions on the scalp and back for the past 2–3 months. There is no history of bone pain or abdominal pain. He has history of bilateral recurrent pneumothoraxes, twice on the right and once on the left side, in the past month. Pleurodesis with povidone iodine is performed on left side and the patient is transferred to your hospital with persistent right pneumothorax with air leak, with an intercostal drainage tube *in situ*. The patient is a never-smoker with no family history of pneumothorax. On general examination, he has small papules, 1–2 mm in diameter, with scaling over scalp and back. Onycholysis, onychoschisis and subungual splinter haemorrhages are present (figure 1).

There is no cervical, axillary or inguinal lymphadenopathy. The abdomen is soft with no hepatomegaly or splenomegaly. Respiratory system examination reveals decreased breath sounds on the right with the intercostal drainage tube *in situ*. The patient is negative for HIV1 and 2 by ELISA.

His 24-h urine volume is 10500 mL and osmolality is 38 mOsm·kg⁻¹. High-resolution computed tomography (CT) of the thorax reveals bilateral cysts (figure 2). His forced vital capacity (FVC) is 1.31 L (37% predicted) and forced expiratory volume in 1 s (FEV₁) is 0.93 L (31% predicted).

Magnetic resonance imaging of the pituitary gland reveals loss of the posterior pituitary bright spot with a thickened stalk showing nodular enhancement. Skeletal plain radiographs are unremarkable. Ultrasound of the abdomen is normal. Whole-body positron emission tomography (PET) does not reveal any fluorodeoxyglucose (FDG)-avid lytic lesions in the bones. Bone marrow aspiration and biopsy are normal.

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Task 1

What is the most likely diagnosis in above case?

- Lymphangioliomyomatosis (LAM)
- Birt-Hogg-Dubé syndrome
- Langerhans cell histiocytosis (LCH)
- Lymphocytic interstitial pneumonia (LIP)





Figure 1 Nails showing a) onycholysis and b) onychoschisis.



Figure 2 High-resolution CT of chest showing bilateral cysts.

Answer 1

c. LCH. A 25-year-old male with diffuse cysts in both lungs, increased urinary output with low urinary osmolality suggestive of diabetes insipidus, and skin and nail lesions favour a diagnosis of LCH [1]. LAM is almost exclusively seen in females and may be associated with angiomyolipoma of the kidney [2]. Birt-Hogg-Dubé syndrome is usually familial, and is usually associated with renal neoplasms and fibrofolliculomas of the midface [3]. LIP is usually seen in Sjögren's syndrome and in those with immunodeficiency disorders [4]. Other differential diagnoses of lung cysts include desquamative interstitial pneumonia, cystic lung metastases, *Pneumocystis jirovecii* pneumonia, tracheobronchial papillomatosis and amyloidosis. Desquamative interstitial pneumonia is seen exclusively in smokers and shows lower lobe predominant ground-glass opacities with cysts with imperceptible walls [5]. Cystic lung metastases may be seen with squamous cell cancers of head and neck [6]. Upper lobe predominant lung cysts may be seen in up to one-third of cases of *P. jirovecii* pneumonia [7]. Lung involvement in tracheobronchial papillomatosis may be in form of nodules that cavitate and form cysts [8]. In nodular forms of amyloidosis subpleural, lower lobe predominant cysts may be seen [9].

Bronchoalveolar lavage shows 88% macrophages, 11% lymphocytes and 1% neutrophils. Aerobic culture does not grow any organism. Transbronchial lung biopsy reveals alveolar tissue lined by epithelial cells showing reactive atypia. Underlying fibrocollagenous tissue shows sheets of atypical cells with moderate eosinophilic cytoplasm and pleomorphic nuclei with inconspicuous nucleoli. Brisk mitosis is noted. The atypical cells express CD45, CD68, CD4 and CD1a. On the basis of clinical, radiological and histopathological findings, a diagnosis of adult-onset multisystemic LCH is made. Right-sided persistent air leak resolves 14 days after intercostal drain (ICD) insertion.

Task 2

Which of the following options is associated with the lowest pneumothorax recurrence rate?

- a. Open thoracotomy with pleurectomy and pleural abrasion
- b. Video-assisted thoracoscopy-guided pleurectomy and pleural abrasion
- c. Surgical chemical pleurodesis
- d. Medical chemical pleurodesis

Answer 2

a. Open thoracotomy with pleurectomy and pleural abrasion. Open thoracotomy with pleurectomy has the lowest recurrence rates (1%) of recurrent pneumothorax. Video-assisted thoracoscopic surgery (VATS) pleurectomy is associated with higher recurrence rates (5%) but shorter hospital admissions and reduced analgesic use. Medical chemical pleurodesis involves instillation of sclerosants like graded talc, tetracycline, povidone iodine or bleomycin into the pleural space *via* a chest drain to cause aseptic inflammation, adhesions and ultimately, pleural symphysis. When the sclerosants are instilled during VATS, it is called surgical chemical pleurodesis [10].

The patient declines surgical interventions. Medical pleurodesis with doxycycline is therefore performed on day 15 of admission. A left-sided pneumothorax developed on day 10 following hospitalisation. Although this completely resolved with ICD placement, pleurodesis was not performed due to tube displacement. As you did not have access to clinical trials for treatment of LCH, the patient is commenced on weekly cycles of vinblastine, and daily oral methylprednisolone, nasal desmopressin and tacrolimus lotion for local application over the nails. The patient is treated with six weekly cycles of vinblastine and daily oral methylprednisolone in tapering doses. As he responds favourably, the induction phase is extended by 6 weeks. In seventh week, the patient reports painful bilateral lower limb paraesthesia. Nerve conduction velocity testing reveals sensorimotor neuropathy.

Task 3

What is the most likely reason for the sensorimotor neuropathy?

- Extrapulmonary manifestation of LCH
- Vinblastine
- Tacrolimus lotion
- Desmopressin

Answer 3

b. Vinblastine. Vinblastine is known to cause dose-dependent sensorimotor neuropathy. Axonal neuropathy is due to disruption of axonal microtubules and interference with axonal transport [11].

A diagnosis of vinblastine-induced peripheral neuropathy is made and its dose is halved. After 12 weeks of the induction phase, the patient is shifted to maintenance regime with three weekly cycles of vinblastine and oral methylprednisolone with daily continuous 6-mercaptopurine. 6 months after induction, he does not have recurrence of pneumothorax, does not develop any new lesions, and his skin and nail lesions have resolved. His lung function improves and now FVC is 1.98 L (45% predicted) and FEV₁ was 1.39 L (37% predicted). On nasal desmopressin, his urine output reduces to 1.5–2 L·day⁻¹. Vinblastine-induced peripheral neuropathy resolves 6 weeks after halving the dose.

Discussion

LCH is a rare disorder characterised by abnormal function and proliferation of histiocytes, which are cells of the mononuclear phagocyte system. Abnormal histiocytes, along with lymphocytes, eosinophils and normal histiocytes, form infiltrates in various organs [1]. It can affect any age group but is better recognised in children. The incidence of LCH among adults is estimated to be 1–2 cases per million [12].

The clinical presentation is diverse and varied, ranging from self-limited lesions to life-threatening disease depending on the organs involved. Of all adult patients registered in the international Histiocyte Society registry, 31% have single-site disease while 69% have multisystemic disease [12]. Bone, skin, liver, ear and lymph node involvement are less common in adults than children. Isolated pulmonary involvement and involvement of genital and oral mucosa are more common in adults than children. Mortality is high if the liver, spleen, central nervous system or bone marrow is involved, and hence these patients are classified as having high-risk LCH [13]. Chest radiography may be normal or may show reticulonodular opacities and cysts. High-resolution CT of the chest reveals nodules, cavitating nodules and cysts with normal intervening lung parenchyma. Cysts predominantly involve the upper and middle lobes but when LCH develops in teenagers, cysts may be lower lobe predominant. In the early stages, only nodules are present, which later cavitate and form cysts. As the disease progresses, cysts coalesce to form irregularly shaped cysts. A skeletal survey with radiographs of the skull, spine, pelvis, and upper and lower limbs is recommended to look for bone lesions. FDG-PET-CT

is needed to detect bony lesions and lesions at other sites [14]. Bronchoalveolar lavage may show $\geq 5\%$ CD1a⁺ cells but has low sensitivity. Transbronchial lung biopsy is diagnostic in 17–50% of cases and may obviate the need of a surgical lung biopsy. Biopsies should be obtained from nodular areas [15, 16]. Histopathological examination shows loosely formed granulomas containing CD1a⁺/CD207⁺ cells especially around small airways [14]. CD1a and CD207 are present on Langerhans cells and they are used as specific markers to distinguish Langerhans cells from other dendritic cell subtypes [17]. *BRAF* V600E genotyping and *MAP2K1* gene sequencing can be performed, as it has been shown that patients with these mutations may exhibit an aggressive course, may show poor response to vinblastine, have high risk of relapse and may benefit from targeted therapy [18, 19]. The patient refuses these investigations due to cost. Biopsy of an extrapulmonary lesion like skin or bone, if present, may also confirm the diagnosis. As your patient complains of polyuria and polydipsia, and as diabetes insipidus is known to occur in LCH, 24-h urinary volume and osmolarity are measured [20]. Diabetes insipidus is due to deficiency of arginine vasopressin due to involvement of the posterior pituitary, which is confirmed in our case by magnetic resonance imaging of brain showing loss of the posterior pituitary bright spot with a thickened nodular stalk.

Pneumothoraxes caused by rupture of subpleural cysts are common and may be recurrent. Definitive management may be challenging, and may involve surgical and/or medical interventions. There are no randomised controlled trials on treatment of adult LCH, so therapeutic regimens have not yet been confirmed. At present, standard chemotherapy regimen for multisystemic LCH in children is the combination of prednisolone (1 mg·kg⁻¹ up to a maximum of 60 mg for 4 weeks) and vinblastine (6 mg·m⁻² up to a maximum of 10 mg every week

for 6 weeks) followed by vinblastine (every 3 weeks) along with prednisolone (first 5 days every 3 weeks) and daily 6-mercaptopurine (30 mg·m⁻² up to a maximum of 50 mg) [20].

Our patient shows a favourable response to the above regime. He does not have any recurrence of pneumothorax, FVC increases, skin lesions resolves and no new lesions appear. Diabetes insipidus, once established, is permanent and our patient requires nasal desmopressin for control of diabetes insipidus [21]. His peripheral neuropathy resolves after reducing the dose of vinblastine.

Pulmonary Langerhans cell histiocytosis (PLCH) is almost exclusively seen in smokers. Our case is a never-smoker. Lung involvement in multisystemic LCH is believed to be due to clonal proliferation of Langerhans cell histiocytes in the lungs. Cigarette smoke plays an important role in pathogenesis of PLCH. Cigarette smoke activates the Langerhans cells in the lung directly and indirectly by stimulating the airway epithelial cells and macrophages to secrete various cytokines and chemokines that cause recruitment, retention and activation of Langerhans cells. These activated Langerhans cells, in certain individuals with favourable host factors, recognise autoantigens in the lung and are responsible for lung parenchymal destruction. Thus, PLCH is due to reactive proliferation of Langerhans cell histiocytes in lung induced by smoking [22]. Unlike PLCH, lung involvement in multisystemic LCH occurs irrespective of smoking status.

Conclusion

Adult LCH is a rare disorder. Lung involvement is common in adults. Unlike PLCH, lung involvement in multisystemic LCH occurs irrespective of smoking status. Diabetes insipidus, once established, is permanent. Management of persistent air leaks can be challenging in these patients.

Affiliations

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Conflict of interest

K. Deokar has nothing to disclose. R. Niwas has nothing to disclose. N. Chauhan has nothing to disclose. N. Dutt has nothing to disclose. P. Jain has nothing to disclose. S. Asfahan has nothing to disclose. R. Kumawat has nothing to disclose.

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