CASE REPORT

A Case Of Multisystemic Langerhans Cell Histiocytosis In An Adult

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ABSTRACT

Langerhans cell histiocytosis is a rare disease in adults with a myriad of clinical presentations. A case of multisystemic Langerhans cell histiocytosis with involvement of bone, skin, lungs, and the hypothalamic-pituitary-axis is reported. The possibility of a disseminated disease should be considered in the diagnosis of Langerhans cell histiocytosis, and these patients should undergo a careful evaluation and follow up with early institution of treatment.

Keywords: Diabetes insipidus, histiocytosis X, pneumothorax

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare granulomatous disorder, characterized by proliferation of the Langerhans (dendritic) cells. Although primarily regarded as a pediatric disease, LCH has been diagnosed in adults as well, who constitute up to 30% to 40% of all cases of LCH[1]. A case of multisystemic LCH in an adult patient seen in our institution is illustrated here.

CASE REPORT

A 23 year old Malay female smoker was transferred to our institution for consideration for lung transplantation during her third episode of pneumothorax in October 2008. She presented in 2007 and mid-2008 with spontaneous pneumothoraces requiring chest tube insertions. A presumptive diagnosis of lymphangioleiomyomatosis (LAM) was made after the HRCT thorax revealed bilateral interlobular septal thickening and multiple thin walled cystic air spaces without lobar predilection, and with preservation of lung volumes, during her 1st admission for pnuemothorax in 2007. She was treated with bronchodilators and steroids after discharge and subsequently underwent Video Assisted Thoracoscopy (VATS) with left pleurectomy after her second pneumothorax in 2008 in attempt to prevent future recurrences. A peri-operative chest X-ray revealed diffuse reticular changes in both lungs with clear costophrenic angles. An old fracture of the right 9th rib was also noted. The pleura biopsy done showed only reactive pleuritis. She also noted new vesicles and ulcerations over her vulval region in the same admission and was empirically treated for HSV infection, although her vulval swabs were subsequently reported as negative for HSV infection. She also underwent a vulval biopsy which only revealed ulceration with granulation tissue on histology.

She presented in October 2008 with acute dyspnoea and chest pain. Emergency endotracheal intubation was undertaken for severe respiratory distress and CXR confirmed the presence of a large left pneumothorax, which was promptly relieved by chest tube drainage and she was extubated 3 days after admission. Subsequent history taking revealed new and worsening symptoms of persistent thirst, polydipsia, polyuria, generalized rash and recurrent vulval ulcerations for the last one year.

* Presented at the 18th SGH Annual Scientific Meeting (Poster Category) 17–18 April 2009

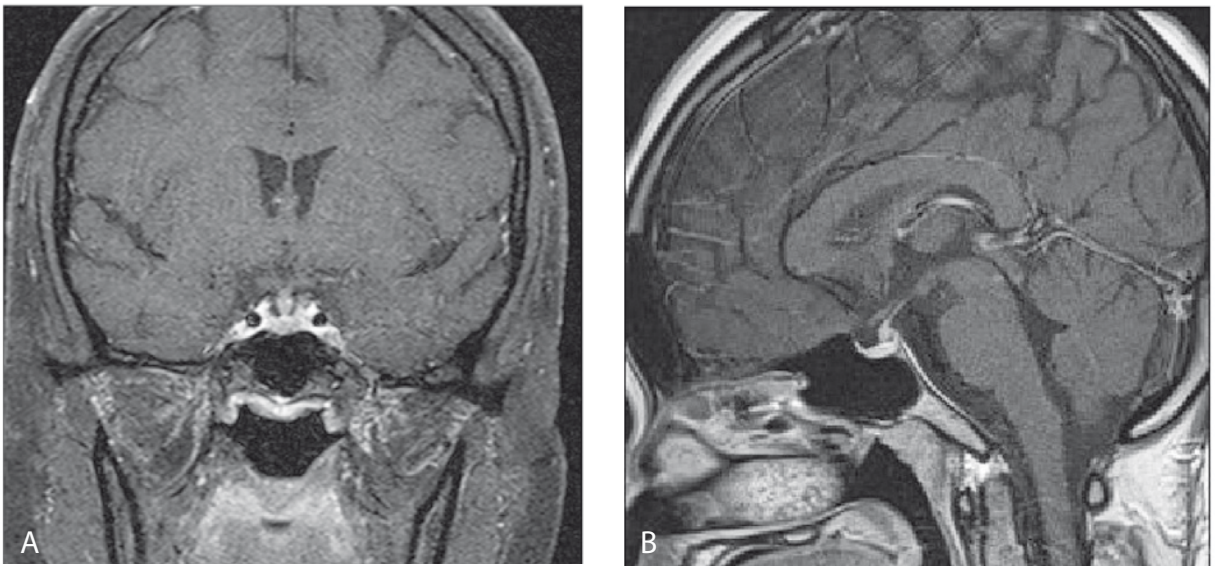

Fig 1 Coronal (A) and Sagittal (B) MRI images of the brain of the patient, showing thickening of the pituitary stalk and loss of the posterior pituitary hyperintense signal

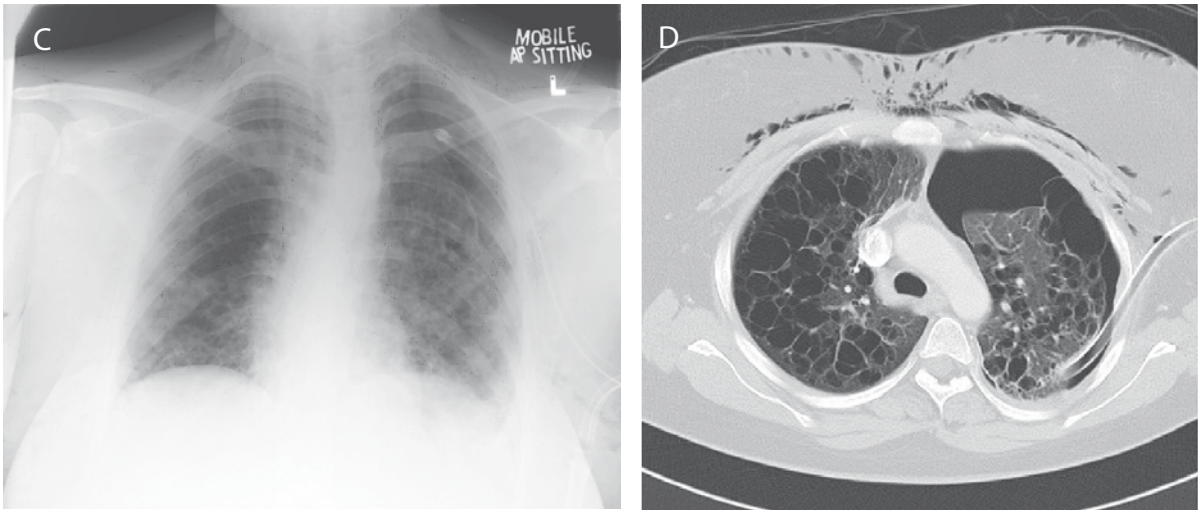

Fig 2 CXR (C) and HRCT thorax (D) of the patient showing extensive cystic lesions of the lungs

On physical examination, she was dehydrated; her blood pressure was 130/90mmHg, heart rate 100 per min. A generalized brown papular skin rash was noted. The rest of her physical examination was normal. Evaluation for possible diabetes insipidus (DI) revealed inappropriate dilute urine with elevated serum sodium; serum sodium 159 mmol/L (NR135-145), serum osmolality 340 mosm/Kg (NR 275-300), urine sodium 19 mmol/L, urine osmolality 168 mosm/kg. Central DI was diagnosed as oral administration of desmopressin yielded an appropriate reduction in the urine output with increased urine concentration with urine output reduced from 250ml/hour to 35ml/hour and urine osmolality increased from 168mosm/Kg to 747mom/Kg 2 hours after administration of 0.1mg oral desmopressin. MRI of the pituitary gland (Fig. 1) demonstrated classical loss of

posterior pituitary hyperintense signal and thickening of the infundibulum in central DI. She had otherwise normal full blood count, serum calcium, fasting glucose, serum cortisol, prolactin, thyrotrophin, free thyroxine, gonadotrophins but a slightly low insulin growth factor level of 102.3UG/L (NR 130-376) UG/L.

The constellation of signs and symptoms in this patient prompted a possible diagnosis of Langerhans cell histiocytosis. A repeat HRCT of the thorax (Fig.2) revealed extensive cystic lesions of the lungs and the abdominal CT was normal except for multiple focal bony defects at T10 vertebra, both ilia and left trochanter suggesting bone involvement. A left thoracotomy with resection of bullae was done for persistent air leak during the admission, but histological examination of the left lung tissue (examined by another pathologist) did not yield significant findings. The diagnosis was eventually confirmed on skin and repeat vulval biopsies demonstrating heavy infiltrates of histiocytes containing abundant foamy to eosinophilic cytoplasm with strong cytoplasmic reaction to S100 and CD1a on immunochemistry tests (Fig. 3 and Fig. 4). She was commenced on high dose oral prednisolone and regular intranasal desmopressin with plans of initiating chemotherapy for treatment of her multisystem disease at a later date.

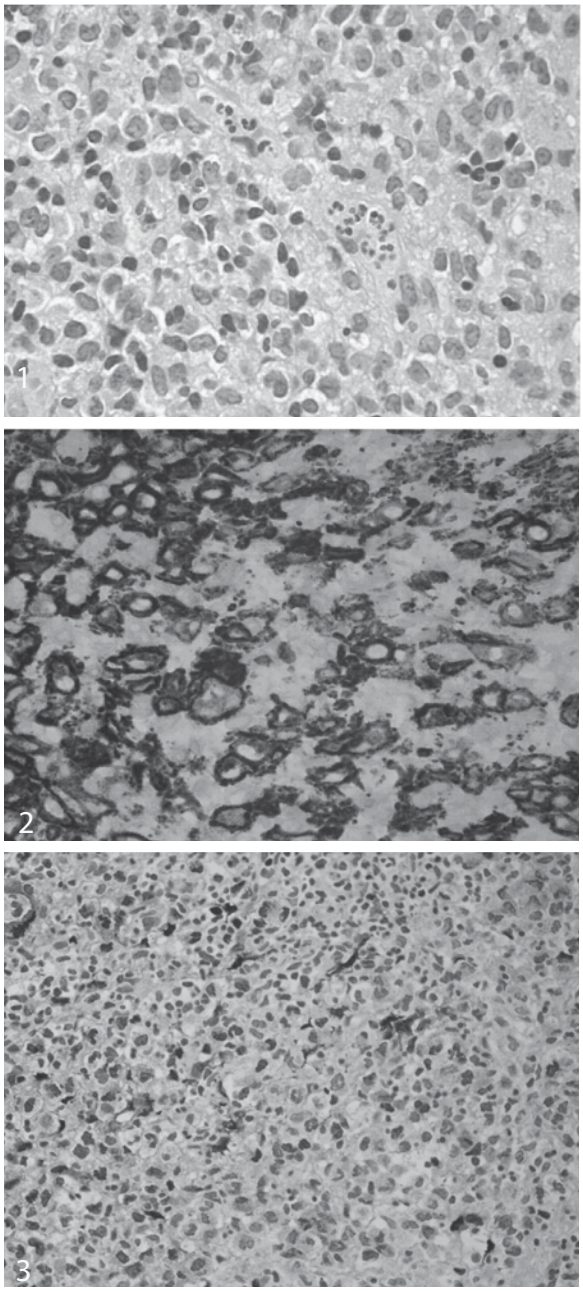

Fig 3 Right axillary biopsy slides (at 40x magnification) demonstrating
(1) dense infiltrates of Langerhans cells, with ovaloid nuclei, foamy cytoplasm and few admixed eosinophils
(2) the Langerhans cells are reactive for CD1a
(3) the Langerhans cells are reactive for S100

DISCUSSION

Langerhans Cell Histiocytosis

The term Langerhans cell histiocytosis (LCH) formerly known as histiocytosis X, encompasses a spectrum of diseases characterized by the proliferation and infiltration of organs by pathological Langerhans cells[1]. The three main clinical entities previously described were eosinophilic granuloma, Hand-Schuller-Christian disease and Letterer-Siwe disease. However, these terms have since been replaced by a classification system developed by the Histiocyte Society[2–3], which incorporated the results of multicentre and randomized trials in children. Depending on the organs involved, LCH has been categorized into localized ("single system disease") and a disseminated form ("multisystem disease"). 'Multisystem disease is further subdivided into two categories ("low risk" and "risk" patients) according to clinical course and response to treatment[4]. The incidence of LCH in adults may reach 1-2 cases per million and is thus significantly lower than in children[5]. According to a published report of 274 patients, the mean age at diagnosis of LCH in adult was 35+ 14yr[6]. It was also noted that diagnosis of LCH was often delayed, with median latency time of 4 months, with 5% of cases spanning 10 years, confirming the rarity of the disease and may be responsible for a suboptimal awareness in some cases[6]. The course of the disease is fairly unpredictable because it can resolve

spontaneously or progress to a disseminated form, compromising vital functions with occasionally fatal consequences[7]. Multisystem LCH is associated with a 20% mortality rate, and 50% of those who survive develop at least one permanent consequence[8–9]. Two different phenotypes are usually seen in adults and children with LCH; involvement of bone, lung, skin and DI usually predominates in adults, whereas involvement of liver, spleen, lymph nodes and bone marrow is more common in children[10].

DI due to pituitary gland involvement, as shown in this patient is one of the most characteristic manifestations of LCH. In majority of cases, the presence of central DI is associated with multisystem disease and is considered to be the most common disease-related permanent consequence[9]. The typical MRI findings of loss of physiologic hyperintense signal ("bright spot") in the posterior pituitary stalk on T1-weighted images, thickening of the pituitary infundibulum or a hypothalamic mass lesion are found in approximately 42% of patients with LCH and central DI[11]. The pathogenesis of DI has been attributed to either infiltration and/or scarring of the HPA, or to an immune process involving reacting antibodies against vasopressin[12]. Established DI is generally permanent and does not respond to any available treatment, except symptomatically.

Pulmonary LCH versus Pulmonary lymphangioleiomyomatosis (LAM)

Most cases of pulmonary LCH occur in young adults between 20 and 40 years of age[13–14]. The near universal association of pulmonary LCH with cigarette smoking strongly implies some causative role[15]. Patients with pulmonary LCH may present with incidental findings on chest radiographs, following a spontaneous pneumothorax or with respiratory or constitutional symptoms, especially weight loss or fever[16]. Pneumothorax with chest pain is the initial clinical manifestation in 15% of patients with pulmonary LCH[17]. The signs and symptoms of pulmonary LCH are often non-specific and often misled the physician into diagnosis of more common pulmonary disorders. However, a history of recurrent pneumothorax coupled with DI or other systemic manifestation of the disease can be helpful in suggesting the diagnosis. A current or past smoking history is a consistent historical feature.

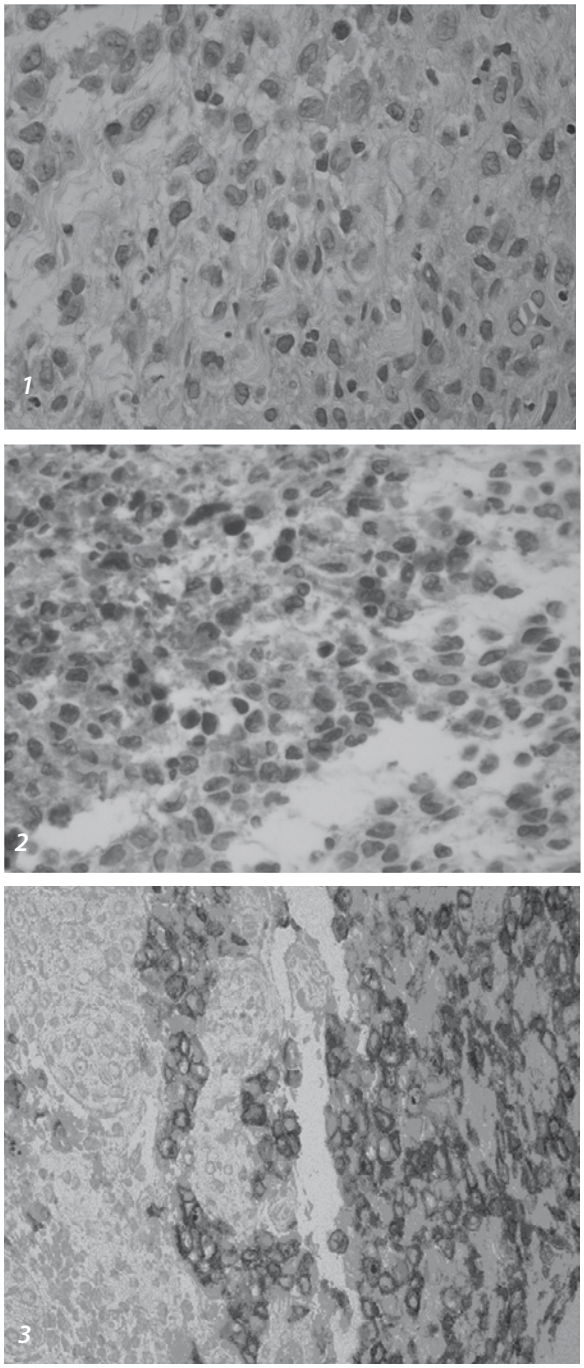

Fig. 4. Right Vulval biopsy slides (at 40x magnification) demonstrating (1) the dendritic cells, which are relatively large, with much cytoplasm that appears slightly foamy. The nuclei are ovoid, with typical longitudinal grooves
(2) the Langerhans cells are reactive for S100
(3) the Langerhans cells are reactive for CD1

A spectrum of radiographic abnormalities such as ill-defined nodules and curvilinear/reticular opacities predominates in most patients[17]. The reticular areas

seen on plain radiographs correspond to areas of superimposed cysts observed on thin-sliced CT[18]. The reticulonodular changes usually predominates mid and upper lung zones. Significant lower lobe involvement such as that seen in this patient's chest radiographs has been reported, but is less common[17]. The costophrenic angles are generally spared and lung volumes are generally preserved or increased[17, 19]. Chest CT findings vary depending on the stage of disease. In disease of recent onset, poorly demarcated micronodular lesions (<5mm) are characteristic. In patients with long standing disease, nodular lesions may be absent and the lung may have cystic or even a pseudoemphysematous appearance[17–18]. Other findings such as absence of mediastinal adenopathy, presence of pneumothorax or lytic rib lesions may be helping in distinguishing pulmonary LCH with other infiltrative lung diseases.

The CT appearance of cysts and nodules adult heavy smoker is virtually diagnostic of pulmonary LCH. However if cysts alone are seen, a distinction has to be made between pulmonary LCH, emphysema (cysts do not have walls) and pulmonary LAM. Pulmonary LAM is a rare disease that affects almost exclusively women of childbearing age. It is characterized by proliferation of atypical smooth muscle like cells with associated cystic changes in the lungs. This progressive destructive process may result in respiratory failure with pneumothorax and chylous pleural effusion[20]. It is associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous syndrome that share molecular etiology with LAM. Both sporadic and TSC related LAM are associated with mutations in tuberous sclerosis genes, which regulate signaling through critical cellular pathways that control energy and nutrient resources in the cell[21–22]. Interestingly, patients with sporadic forms of LAM (not associated with TSC) may have some extra-pulmonary manifestations found in TSC, such as renal angiomyolipomas, axial lymphadenopathy and abdominal lymphangiomyomas[23–25]. In a national registry which enrolled 243 patients with LAM, average age of onset of symptoms was 39 years, approximately 60% were premenopausal and 60% were non smokers[20]. TSC was present in 15% of patients. In general, the diagnosis should be strongly suggested in any young women who presents with emphysema, recurrent pneumothorax, or a chylous pleural effusion. HRCT can often confirm the diagnosis, and tissue confirmation may not always be necessary[26–27]. LAM tends to be uniformly involving all regions of the lungs and does not spare the costophrenic angles, features unusual for pulmonary LCH[28]. The findings of diffuse, homogenous, small (less than 1cm diameter) thin walled cysts can be highly suggestive of the diagnosis in an appropriate clinical context.

In the patient described, the initial presentation of recurrent pneumothorax without systemic manifestations of LCH has led to the initial diagnosis of pulmonary LAM. The multiple thin walled cysts on HRCT thorax could suggest possible LAM versus late pulmonary LCH, which is unusual for this patient, considering her young age. However, in retrospect, the appearance of the persistent vulval lesions, lesions sparing the costophrenic angles and an incidental old rib fracture on the chest radiograph may have suggested the possibility of LCH. The history of smoking and the absence of features associated with TSC may have helped to differentiate LCH from LAM.

Nonetheless, it was the appearance of systemic clinical features associated with LCH that prompted re-examination of the initial diagnosis. The involvement of the other organ systems (posterior pituitary, skin, mucous membranes and bone involvement) made LCH a more likely diagnosis than LAM, which was later confirmed on histology.

The natural history of pulmonary LCH is variable, with some patients experiencing spontaneous remission of symptoms and others progressing to end stage fibrotic lung disease. Most subjects demonstrate gradual progression with continue cigarette smoking, while the disease may regress with cessation of smoking[29]. Therapeutic options for LCH in general include watchful waiting, local treatment, immunomodulation, irradiation, chemotherapy, and liver, lung and allogenic stem cell transplantation in advanced disease stage 4. Lung transplantation should be considered in patients with advanced, progressive pulmonary disease unless contraindications are present. Patients with limited LCH disease have an excellent prognosis, usually without the need for systemic therapy. In contrast, patients with multifocal skeletal involvement, refractory cutaneous lesions, disseminated or recurrent disease will nearly always benefit from systemic

therapy. The optimal treatment strategy in LCH patients, however, remains to be defined.

CONCLUSION

Langerhans cell histiocytosis is a rare disease in adults with a myriad of clinical presentations. Diagnosis requires a strong suspicion of this disease entity. This case report showed that a premenopausal woman, with an initial diagnosis of pulmonary LAM based on HRCT findings and recurrent pneumothraces, was eventually confirmed to have multisystem LCH when other associated clinical features subsequently surfaced. Physicians should be cautious of the common pitfalls in the diagnosis of these two conditions.

ACKNOWLEDGEMENT

Special thanks to Dr Victor Ng Weng Leong from the Department of Pathology, Changi General Hospital for providing the histology slides of this patient.

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