Langerhans cell histiocytosis with hypogonadotrophic hypogonadism

Ong C W M, Chua L S, Ng A, Low S Y

ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease characterised by monoclonal proliferation and infiltration of organs by large mononuclear cells. Organs commonly involved include the lungs and pituitary gland. However, the disease association with hypogonadotrophic hypogonadism has not been reported in the literature, to our knowledge. We report a 26-year-old Chinese man with LCH, recurrent pneumothoraces, diabetes insipidus and hypogonadotrophic hypogonadism. The clinical features and management of the disease are reviewed.

Keywords: diabetes insipidus, hypogonadotrophic hypogonadism, interstitial lung disease, Langerhans cell histiocytosis

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a disease characterised by monoclonal proliferation and infiltration of organs by large mononuclear cells. It is classically associated with diabetes insipidus. However, reports of its association with hypogonadotrophic hypogonadism have never been reported. We report a case of LCH in a man who presented with recurrent pneumothoraces and had both diabetes insipidus and hypogonadotrophic hypogonadism.

CASE REPORT

A 26-year-old Chinese man, previously fit, presented with a one-day history of right-sided pleuritic chest pain associated with dyspnoea at rest. There was no associated cough or fever. He had experienced a similar episode four years ago and was diagnosed to have a left pneumothorax. He was initially treated with chest tube drainage but subsequently required a video-assisted thoracoscopic surgery (VATS) with pleurodesis, and lung biopsy for persistent air-leak. He was discharged and had been well since. There was no family history of lung disease. He started smoking 6–7 cigarettes per day at 17 years of age, for five years until his first pneumothorax.

Fig. I Chest radiograph shows a right pneumothorax. The lung volumes are normal with diffuse reticulonodular shadows and interstitial infiltrates throughout both lung fields.

He then stopped smoking for two and a half years before restarting on ten cigarettes per day, for the subsequent two years, till this presentation. He was single and had no family history of hypogonadism and Kartagener's syndrome.

Clinical examination revealed decreased breath sounds in the right lung base and there was no dextrocardia. In addition, he had sparse pubic and axillary hair, and small testes. Laboratory investigations were notable for serum sodium of 151 (normal range [NR] 135–145) mmol/L, serum osmolality of 291 (NR 275–301) mmol/kg, urine osmolality of 47 (NR 50–1,200) mmol/kg and spot urine sodium < 10 mmol/L. On direct questioning, he admitted to experiencing polydipsia, polyuria and nocturia, causing interrupted sleep for the past year. He shaved once every two weeks. An endocrinology referral was made, and a water deprivation test was performed (Table I). Hormonal profile showed that he had hypogonatrophic hypogonadism: follicular stimulating hormone 1.9 (NR 1.2–8.1) U/L, luteinising hormone < 0.5 (NR 2.0–10.9) U/L and total testosterone 0.36 (NR 6.1–27.1) nmol/L.

Division of Infectious Diseases, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074

Ong CWM, MBBS, MMed, MRCP
Registrar

Department of Respiratory and Critical Care Medicine

Chua LS, MBBS
House Officer

Low SY, BA, BMBCh, MRCP
Consultant

Department of Endocrinology

Ng A, MBBS, MMed, MRCP
Associate Consultant

Correspondence to:
Dr Catherine WM Ong
Tel : (65) 6772 4362 / 4380
Fax : (65) 6779 4361
Email: catongwm@yahoo.com

Table I. Results of the water deprivation test.

Time	Hours	Weight (kg)	BP (mm/Hg)	Urine vol. (ml)	Urine Osm (mmol/kg)	Plasma Osm (mmol/kg)	U:P ratio	Serum Na (mmol/L)
0800	0	59	131/88	820	53	306	0.176	146
0900	1	58	124/80	520	65	310	0.209	148
1000	2	57.5	127/81	450	78	308	0.25	150
1100*	3	57	125/96	380	85	314	0.27	152
1200	4	59	130/76	30	556	285	2.06	137
1300	5	62	120/74	32	414	289	1.71	137
1400	6	61	120/75	30	510	291	1.75	139
1500	7	61	110/60	38	795			
1600	8	61	100/80	55	532			
2000	12							133
0600	22							135

BP: blood pressure; Na: sodium; Osm: osmolality; U:P: urine-to-plasma osmolality; vol: volume
*Intramuscular desmopressin (DDAVP) was administered at the third hour (1100 hours), resulting in an increased concentration of the patient's urine, leading to a rise in urine osmolality and a concomitant fall in urine output of more than 100%, consistent with complete central diabetes insipidus.

Serum prolactin was 37.6 (NR 5.0–27.7) Ug/L, free T4 13.9 (NR 9.6–19.1) pmol/L, thyroid-stimulating hormone 0.46 (NR 0.36–3.24) mIU/L and synacthen test was normal.

Magnetic resonance imaging of the pituitary showed loss of the normal high T1-weighted signal in the posterior pituitary, a thickened posterior stalk and prominent enhancement in the post-contrast images, in keeping with LCH, involving the hypothalamic pituitary axis with diabetes insipidus. Chest radiograph (Fig. 1) revealed a right pneumothorax. The lung volumes were normal with diffuse reticulonodular shadows and interstitial infiltrates throughout both lung fields. A chest tube was inserted and a high-resolution computed tomography (CT) of the thorax (Fig. 2) was subsequently done. It showed bizarre, thin-walled cysts and nodules in both lungs, with relative sparing of the lung bases.

The patient underwent a VATS of the right lung with pleurodesis and lung biopsy. The whole right lung was found enveloped in a film of fibrous tissue with dense adhesions at the upper half of the chest cavity. Pathology of the lung biopsy (Fig. 3) revealed peribronchiolar fibrosis with stellate and irregular configuration. There were small aggregates of cells containing nuclear grooves which were positive for CD1a and S100 immunostains. The patient was discharged soon after surgery and was started on intranasal desmopressin (DDAVP) with cessation of nocturia. He was able to have uninterrupted sleep. There were plans to start him on testosterone replacement to avert early osteoporosis.

Respiratory-wise, he returned to work and was able to climb three flights of stairs. Pulmonary function test performed two months postoperatively, showed a forced expiratory volume (FEV1) of 1.71 (48.6% predicted), forced vital capacity (FVC) of 2.34 (53.8% predicted), and FEV1/FVC ratio of 72.94%. Residual volume (RV) was 2.11 (66.5% predicted), total lung capacity (TLC) was 4.44 (80.1% predicted) with RV/TLC ratio of 47.57%. Diffusion capacity (DLco) was decreased at 40% predicted. This demonstrated a mixed obstructive and restrictive pattern on spirometry and lung volumes, with evidence of air-trapping and a moderately reduced diffusion coefficient.

DISCUSSION

LCH is a disease characterised by monoclonal proliferation and infiltration of organs by large mononuclear cells.[1] It is known by a variety of names; eosinophilic granuloma is a term used if the disease is confined to the bones, whereas with systemic involvement, the term, systemic histiocytosis X is used. The aggressive systemic form of the disease is termed Letterer-Siwe disease, and if there is a triad of exophthalmos, diabetes insipidus with bone lesions, it is named Hand-Schuller-Christian disease. Organs commonly involved include the lungs, bones, pituitary gland and skin.[2] It is a rare disease, with incidences reported at less than 5% of patients with interstitial lung disease,[3] and occur mainly among Caucasians.[4,5] It has equal incidence among both genders.[4] Smoking has been attributed to be associated with the disease, with reports of up to 90% of patients being smokers.[4,6] It is postulated that cigarette smoke activates Langerhans cells to secrete bombesin-like peptides, causing secretion of cytokines. These in turn result in the formation of lung nodules and fibrosis.[7] Two diagnostic features of Langerhans cell include identifying the CD1a antigen via immunohistochemical stains on the cell surface under light microscopy,[8] or identifying Birbeck granules under electron microscopy.[9] Histological diagnosis of pulmonary LCH rests on

Fig. 2 High-resolution CT image of the thorax shows bizarre, thin-walled cysts and nodules in both lungs. There is relative sparing of the lung bases. The right pneumothorax is present with the chest tube in place.
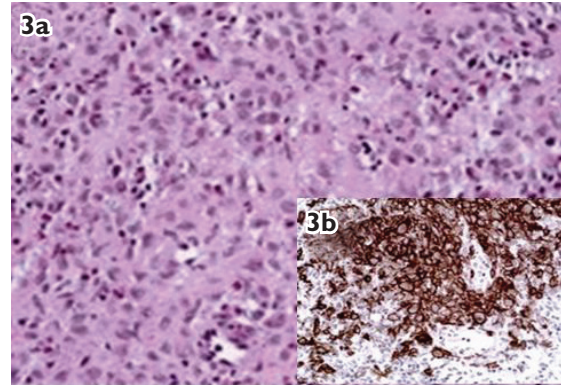

Fig. 3 (a) Photomicrograph shows peribronchiolar fibrosis with stellate and irregular configuration (Haematoxylin & eosin, × 200). (b) Inset. There are small aggregates of cells containing nuclear grooves which are positive for CD1a immunostains (brown pigments).

identifying typical lung lesions and increased numbers of Langerhans cells. Lung involvement may occur alone or as part of a multiorgan disease. Patients can present with a nonproductive cough, dyspnoea or manifest a pneumothorax. They can also present with constitutional symptoms such as weight loss, fever and night sweats.[10] Other symptoms to suggest extrapulmonary involvement include bone pain, polyuria and polydipsia as a result of diabetes insipidus, or a rash due to cutaneous involvement.[10] Interestingly, our patient also presented with signs of hypogonadism, and to our knowledge, this is the first case reported in association with LCH.

Chest radiograph abnormalities include bilateral interstitial infiltrates and cystic changes, typically sparing the costophrenic angles.[4] Honeycombing is often seen on the chest radiograph, with normal lung volumes. High resolution CT is a sensitive tool in the diagnosis of pulmonary LCH. Findings may reveal nodular and cystic changes occurring predominantly in the middle and upper lobes.[11] Pulmonary function tests are either normal, or demonstrate obstructive, restrictive or mixed abnormalities. Carbon monoxide diffusion capacity reduction is a consistent abnormality.[4,5]

Confirmation of diagnosis may be made by surgical lung biopsy, bronchoalveolar lavage or transbronchial lung biopsy. An open lung biopsy is the gold standard and has the highest yield among the three methods to diagnose LCH.[12] The presence of increased numbers of Langerhans cells, > 5% in the bronchoalveolar-lavage fluid, strongly suggests pulmonary LCH.[13] Transbronchial lung biopsy has a low yield of 10%–40% for diagnosis of this disease.[10]

An essential part of treatment is smoking cessation, with reports of radiological and physiological improvement of lung function of the disease.[14]

There have been reports on the use of steroids and immunosuppressive therapy,[15] but no consensus exists on when steroid therapy should be commenced. Small case series have suggested stabilisation and improvement of the disease with such treatments.[4,6] Severe cases may even warrant lung transplantation.[10] It is imperative that patients should cease smoking before lung transplant as there is evidence of recurrence of the disease if smoking were to resume.[16] Adverse prognostic factors include extremes of age, multiorgan involvement, florid radiographical changes and decreased diffusion lung capacity.[5] Adults with pulmonary LCH may be at an increased risk for malignancy,[10] such as lymphoma and bronchial carcinoma. Hence, it is important to be vigilant when patients present with constitutional symptoms.

LCH remains a rare and diverse disease. It generally follows a benign course, although it may cause considerable morbidity due to both the disease itself and its treatment. Smoking cessation remains the cornerstone of treatment for pulmonary LCH. Patients who are at risk of rapidly progressive disease should be identified early so that an appropriate treatment plan can be instituted.

REFERENCES

1. Nezelof C, Basset F. Langerhans cell histiocytosis research. Past, present, and future. Hematol Oncol Clin North Am 1998; 12:385-406.
2. Howarth DM, Gilchrist GS, Mullan BP, et al. Langerhans cell histiocytosis: diagnosis, natural history, management and outcome. Cancer 1999; 85:2278-90.
3. Gaensler EA, Carrington CB. Open biopsy for chronic diffuse infiltrative lung disease: clinical, roentgenographic, and

physiological correlations in 502 patients. Ann Thorac Surg 1980; 30:411-26.

4. Friedman PJ, Liebow AA, Sokoloff J. Eosinophilic granuloma of lung. Clinical aspects of primary histiocytosis in the adult. Medicine (Baltimore) 1981; 60:385-96.

5. Basset F, Corrin B, Spencer H, et al. Pulmonary histiocytosis X. Am Rev Respir Dis 1978; 118:811-20.

6. Schönfeld N, Frank W, Wenig S, et al. Clinical and radiologic features, lung function and therapeutic results in pulmonary histiocytosis X. Respiration 1993; 60:38-44.

7. Aguayo SM, Kane MA, King TE Jr, et al. Increased levels of bombesin-like peptides in the lower respiratory tract of asymptomatic cigarette smokers. J Clin Invest 1989; 84:1105-13.

8. Birbeck MS, Breathnach AS, Everall JD. An electron microscope study of basal melanocytes and high-level clear cells (Langerhans cells) in vitiligo. J Invest Dermatol 1961; 37:51-64.

9. Tazi A, Bonay M, Grandsaigne M, et al. Surface phenotype of Langerhans cells and lymphocytes in granulomatous lesions from patients with pulmonary histiocytosis X. Am Rev Respir Dis 1993; 147:1531-6.

10. Vassallo R, Ryu JH, Colby TV, Hartman T, Limper AH. Pulmonary Langerhans'-cell histiocytosis. N Engl J Med 2000; 342:1969-78.

11. Brauner MW, Grenier P, Mouelhi MM, Mompoint D, Lenoir S. Pulmonary histiocytosis X: evaluation with high-resolution CT. Radiology 1989; 172:255-8.

12. Colby TV, Lombard C. Histiocytosis X in the lung. Hum Pathol 1983; 14:847-56.

13. Auerswald U, Barth J, Magnussen H. Value of CD-1-positive cells in bronchoalveolar lavage fluid for the diagnosis of pulmonary histiocytosis X. Lung 1991; 169:305-9.

14. Mogulkoc N, Veral A, Bishop PW, et al. Pulmonary Langerhans' cell histiocytosis: radiologic resolution following smoking cessation. Chest 1999; 115:1452-5.

15. Arico M, Girschikofsky M, Généreau T, et al. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. Eur J Cancer 2003; 39:2341-8.

16. Habib SB, Congleton J, Carr D, et al. Recurrence of recipient Langerhans' cell histiocytosis following bilateral lung transplantation. Thorax 1998; 53:323-5.