CASE REPORT

Complete remission of nodular pulmonary Langerhans cell histiocytosis lesions induced by 2-chlorodeoxyadenosine in a non-smoker

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Received 31 July 2007; accepted 3 September 2007
Available online 1 November 2007

KEYWORDS
Langerhans cell histiocytosis; Cigarette smoking; 2-Chlorodeoxyadenosine; Interstitial lung disease; Lung nodules

Summary
Pulmonary Langerhans cell histiocytosis (LCH) is an uncommon cause of interstitial lung disease. Corticosteroids and chemotherapeutic agents are frequently used to treat symptomatic patients but their efficacy is unclear. We describe a 66-year-old with biopsy-proven pulmonary and systemic LCH, whose pulmonary abnormalities responded dramatically to treatment with 2-chlorodeoxyadenosine (2-CdA). We propose that, in selected cases, 2-CdA should be considered in the management of pulmonary LCH.

Introduction
Treatment options for patients with pulmonary Langerhans cell histiocytosis (LCH) are limited. Herein, we report a case of LCH with unusual pulmonary manifestations occurring in a non-smoker. The radiographic findings in this case illustrated multiple lung nodules of varying dimensions without upper lobe predominance and without cystic change. Both pulmonary and other manifestation of LCH responded completely to therapy with systemic 2-chlorodeoxyadenosine (2-CdA).

Case report
The patient, a 66-year-old never smoker, initially presented at another facility because of pain in the shoulder and back. Physical examination revealed cervical lymphadenopathy but no other features. A computed tomogram (CT) of the
chest demonstrated left cervical lymphadenopathy, several discrete pulmonary nodules (ranging in size from a few mm to 3 cm in diameter—Figure 1). There were no cystic changes on the chest CT. A deep cervical lymph node biopsy showed diffuse infiltration by S100 and CD1a positive Langerhans cells, consistent with a diagnosis of LCH (Figure 2A). Bronchoscopy and transbronchial biopsies were performed to evaluate further the lung findings. Transbronchial biopsy of the 3 cm mass in the right lower lobe demonstrated LCH (Figure 2B). Histopathology of the lymph node and bronchoscopic lung biopsy were reviewed by two expert lung pathologists (M.C.A. and J.L.M.) and deemed to have diagnostic features of LCH. Pulmonary function testing and gas exchange were normal. Due to the history of back pain, a spinal MRI was obtained. This demonstrated lesions involving multiple vertebral bodies in the cervical and thoracic regions. He was subsequently started on systemic chemotherapy with 2-CdA at a dose of 5 mg/m² delivered over a 5-day period once a month for 4 months to complete four cycles. The treatment was well tolerated with minimal toxicity. Following treatment, the patient experienced resolution of back pain, and CT of the chest demonstrated complete resolution of the lung lesions, including the 3 cm mass in the right lower lobe (Figure 3). Follow-up MRI of the spine demonstrated marked improvement in the abnormal enhancement of multiple vertebral bodies noted in the MRI obtained at presentation.

Discussion

LCH is an uncommon but important cause of lung disease that may also affect the reticuloendothelial system, bones, nervous system, skin, and other organs. Although compelling evidence implies cigarette smoking as a cause of isolated pulmonary LCH, the association between smoking and pulmonary LCH in patients with multi-system LCH is unclear. For instance, whereas 90% of patients with isolated forms of pulmonary LCH are either current or former smokers, less than half of adults with multi-system LCH are smokers. The current case report confirms that smoking is not obligatory for the development of pulmonary LCH (at least in the context of multi-system disease), as there was no evidence for either primary or second-hand tobacco exposure.

The radiographic findings in pulmonary LCH have been described as characteristic when combinations of cystic and nodular abnormalities occur with preferential distribution to the upper and mid-lung zones. Although this pattern predominates, in certain instances the CT may reveal other patterns of involvement that suggest alternative diagnoses. The current report illustrates an unusual radiographic presentation of pulmonary LCH with multiple lung nodules of varying sizes distributed in both lungs, and a 3 cm mass in the right lower lobe (Figure 1). This radiographic appearance is more consistent with a metastatic malignancy, which must be carefully ruled out since LCH has been repeatedly described to predate, co-exist, or occur following the diagnosis of various malignancies. Although lung nodules are a characteristic feature of pulmonary LCH, nodules are typically a centimeter or less in size, and it is distinctly unusual to see discrete large nodules such as occurred in our patient.

Treatment of adults with LCH may be challenging. While smoking cessation is imperative for all patients with smoking-related pulmonary LCH, treatment decisions in non-smokers with pulmonary LCH should be based on determination of the degree of lung impairment together with careful assessment of disease burden in other organ systems. The roles of immunosuppressive medications and chemotherapy in the management of adult pulmonary LCH in either smokers or non-smokers are unclear. In our patient, the decision to treat was based primarily on vertebral involvement which may have led to spinal cord compromise. Use of 2-CdA was considered appropriate because of published evidence demonstrating efficacy in adult patients with refractory LCH, and the relatively limited toxicity associated with 2-CdA therapy in adults with LCH (personal observations). A trial with high-dose corticosteroids was not pursued because of limited efficacy and significant adverse effect profile. The patient had an excellent response to 2-CdA with no evidence of LCH in lungs, spine or lymph nodes at 18 months of follow-up. Although there are no definitive recommendations for long-term follow-up, it is our practice to obtain 6-monthly CT of the chest for the first

Figure 1  Chest computed tomogram at the time of presentation showing a 1 cm nodule in the posterior aspect of the left upper lobe (upper panel) and a 3 cm mass in the right lower lobe (lower panel).
12 months after completion of treatment, and subsequently obtain annual CT for at least an additional 2 years to ensure a sustained response. Combinations of prednisone and vinblastine have also been described as effective, particularly in the management of childhood LCH, and a prospective multi-center trial conducted by the International Histiocyte Society (http://www.histio.org) will be testing the effect of this combination on the lung function of patients with pulmonary LCH who progress despite smoking cessation.

2-CdA is a purine nucleoside analog that causes lymphocyte and monocyte apoptosis (see comprehensive current review on 2-CdA by Robak et al.1). The efficacy of 2-CdA in the management of pulmonary LCH in our patient does not imply that it should have similar efficacy in cigarette smoking-related pulmonary LCH, that accounts for the majority of pulmonary LCH encountered by the pulmonary specialist. It is probable that the pathobiology of smoking-related pulmonary LCH is distinct from other forms of pulmonary LCH occurring in non-smokers. This contention is
partly supported by studies on LCH tissue biopsies obtained from patients with systemic forms of LCH that demonstrate clonal expansion, whereas lesional cells in the isolated form of pulmonary LCH are expanded in a polyclonal fashion suggestive of an antigenically driven response, potentially to some as yet unknown component in cigarette smoke. Ultimately, the role of 2-CdA in the management of pulmonary LCH remains to be demonstrated by prospective studies. There are currently no effective interventions that prolong survival in patients with progressive pulmonary LCH, other than transplantation in selected cases. With the response our patient had, we propose that 2-CdA should be considered as a therapeutic option in patients with progressive pulmonary LCH.

Conflict of interest

The authors have no competing interests to declare. The manuscript has been reviewed and approved by all authors.

Acknowledgment

Supported by a research grant from the American Histiocytosis Association to R.V.

References


Figure 3 The follow-up chest computed tomogram obtained 9 months after presentation and following completion of four cycles of 2-CdA therapy showed almost complete resolution of the nodules observed at presentation.