Spontaneous Regression of Pulmonary Involvement after Smoking Reduction and Removal of and Radiation Therapy for Langerhans Cell Histiocytosis of the Sphenoid Bone: Which Comes First, the Chicken or the Egg?

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Abstract

Isolated pulmonary Langerhans cell histiocytosis (LCH) in adults is known to regress spontaneously after smoking cessation alone, but little is known about whether this rationale could also apply in cases of multisystem pulmonary LCH. In particular, pediatric patients with multisystem LCH including involvement in “risk organs” such as lungs often benefit from systemic chemotherapy. Here, we present a 37-year-old man with spontaneous regression of pulmonary lesions in multisystem LCH, achieved solely by smoking reduction following local treatment of bone lesions.

Key words: multisystem pulmonary LCH, adult onset, eosinophilic granuloma of lung, extrapulmonary involvement


Introduction

Langerhans cell histiocytosis (LCH) was formerly known as histiocytosis X, which includes eosinophilic granuloma (a benign form of tumor localized to bones or lungs), Hand-Schüller-Christian disease (a chronic form presenting with a classic triad of skull lesions, exophthalmos, and diabetes insipidus), and Letterer-Siwe disease (an aggressive form with multi-organ involvement) (1). Although bone, especially the skull, is the most commonly affected organ in LCH, previous studies on children, the age group that LCH predominantly affects, revealed that the prognosis depends on the type and number of systems involved (2-5). Single-system disease with unifocal or multifocal lesions within a single organ such as skin, bone, and lymph nodes generally has a good prognosis with low mortality, although some cases require minimal treatment interventions such as surgical curettage, irradiation, or mild chemotherapy. In contrast, multisystem disease involving ≥2 organs, especially including any “risk organs” (liver, lungs, spleen, and bone marrow), carries a worse prognosis in terms of morbidity and mortality.

In this report, we describe an adult patient with multisystem LCH in whom pulmonary lesions spontaneously regressed solely by smoking reduction after local treatment of a solitary bone lesion. An international study in children with multisystem LCH reported that intensive chemotherapy could improve outcomes, up to approximately 75% on 5-year survival in a risk group involving “risk organs” (5). Conversely, an international registry study stated that despite no treatment in 31% of adult patients with multisystem LCH, 5-year survival was 91.7% (6). The high prevalence of survival provided little incentive to administer chemotherapy agents in our asymptomatic patient without organ dysfunction. Based on this case, we also discuss the pathogenesis and management of multisystem pulmonary LCH in adults.
Case Report

A previously healthy 37-year-old man presented with right temporal headache. Physical and neurological examinations and laboratory tests were unremarkable. Magnetic resonance imaging of the head showed a solitary tumor of the right sphenoid bone (Fig. 1A, 1B, arrows). Pulmonary function tests were normal. Hence a preoperative diagnosis of meningioma was made, and surgical removal of the tumor was performed. The tumor specimen was shown to contain oval tumor cells with grooved nuclei and fine chromatin by Hematoxylin-Eosin staining (Fig. 2A), which expressed CD1a (Fig. 2B), S100 protein (Fig. 2C), and CD68 (Fig. 2D) with characteristic pathological findings.

Figure 1. Magnetic resonance imaging of the brain revealed a solitary tumor of the right sphenoid bone (A and B, arrows).

Figure 2. Pathological examination of the tumor specimen. Oval tumor cells with grooved nuclei and fine chromatin were seen by Hematoxylin and Eosin staining (A), with many infiltrating eosinophils that formed abscesses, so-called eosinophilic granulomas, with Charcot-Leyden crystals (A, arrows). Immunohistochemical stains for CD1a (B), S100 protein (C), and CD68 (D) are positive, confirming the diagnosis of Langerhans cell histiocytosis.
Figure 3. Chest computed tomography showed multiple nodules with or without cavitation measuring <10 mm in diameter which were predominantly distributed in the upper and middle fields of both lungs on diagnosis (A-C, arrows). Only one nodule remained on follow-up CT scans after 4 years (D-F, arrows).

(Fig. 2D). In the background, we observed many infiltrating eosinophils that formed abscesses, so-called eosinophilic granulomas, with Charcot-Leyden crystals (Fig. 2A, arrows). These findings are characteristic of LCH. Chest computed tomography showed multiple nodules with or without cavitation measuring <10 mm in diameter and predominantly distributed in the upper and middle fields of both lungs (Fig. 3A-3C, arrows). Based on these findings, along with a smoking history of 2 packs of cigarettes per day since the age of 22, a diagnosis of multisystem LCH involving the lungs and a single bone was made. The results of laboratory tests after operation were within normal limits as follows: white blood cell count, 5,310/mm$^3$; erythrocyte sedimentation rate, 3 mm/hr; lactate dehydrogenase, 160 U/L (normal range 119-229); C-reactive protein, 0.1 mg/dl; soluble interleukin-2 receptor, 372 U/ml (normal range 220-530); KL-6, 307 U/ml (normal range 0-499). Because the patient was asymptomatic, local irradiation of 18 Gy was administered to the operative site of the right sphenoid bone. Rather than smoking cessation, the patient only reduced his smoking habit to one pack of cigarettes (1 mg tar) per day. On high-resolution chest CT scans obtained 3 months after smoking reduction, we observed regressed nodules with or without cavitation. Four years later, the patient remains asymptomatic, with only one nodule of approximately 2 mm in diameter in the right upper lobe on follow-up CT scans (Fig. 3D-3F, arrows).

Discussion

Adult patients with LCH are more likely to present with isolated pulmonary disease when compared with children, and disease pathogenesis strongly correlates with heavy smoking (3, 6-9). Typical CT findings are multiple nodules with or without cavitation predominantly in the upper and middle lobes in the early stages, which become cystic and fibrotic as the disease progresses (10). This finding could aid the diagnosis of pulmonary LCH in the present patient although pathological examination by bronchoscopy was not performed. While the course of pulmonary LCH in adults is variable and unpredictable, ranging from spontaneous regression to progressive relentless disease leading to respiratory failure and death over a period of months, 5-year survival is 74.6-87.8% (6, 8). In most patients, especially those who are asymptomatic in the early stage of isolated pulmonary LCH, smoking cessation without other treatment interventions can improve or maintain clinical and radiographic findings with regard to pulmonary involvement (11, 12). Although bone lesions are the most common extrapulmonary involvement in multisystem pulmonary LCH in adults, little information is known about their appropriate management (3, 6-9). In the present case, the bone tumor burden was reduced by surgical curettage which is a potential curative therapy. The significance of local low-dose radiation is controversial, especially in multisystem LCH. However, we decided to add it in substitution for systemic chemotherapy, based on reference to a previous report that local radiation therapy alone or after surgical excision was very successful treatment of the solitary bone lesion (3). The aim of treatment in LCH is to reduce mortality and to prevent acute morbidity, disease reactivation, and permanent consequences. Hence, close observation with radiographic surveillance was
considered important to monitor unpredictable recurrent or progressive disease in the present patient.

The pathogenesis of extrapulmonary involvement in our case remains unclear. In LCH lesions, pathologic dendritic cells (LCH cells) that express CD1a, which is highly specific for Langerhans cells of the skin, proliferate and accumulate along with various other cells (e.g., eosinophils, T cells, macrophages, and osteoclast-like multinucleated giant cells) (2). Normal, terminally differentiated Langerhans cells do not proliferate but migrate to lymph nodes, where they present antigens to T cells after exposure to antigens and cytokines. In children, LCH cells spread to almost any organ and clonally proliferate in most lesions of multisystem LCH (13); however, some smoking-related pulmonary LCH lesions in adults primarily show polyclonal expansion (14). Furthermore, LCH cells lack recurrent genomic abnormalities (15). To summarize, the main question of whether the accumulation of LCH cells is a result of an intrinsic defect of their progenitors (neoplastic change) or is caused by an inappropriate external stimulus, such as cytokines in the local microenvironment or serum (a reactive process), remains unanswered (2, 16, 17). If, in the present case, outgrowth from a primary pulmonary LCH lesion caused by long-lasting exposure to cigarette smoking-associated antigens would give rise to a secondary bone lesion, smoking reduction might be highly effective. However, while the present patient would not stop smoking after a 15-year smoking history, pulmonary lesions which rapidly regressed within 3 months after operation remain in remission. This fact suggests that smoking was associated with more development of pulmonary lesions by recruitment of LCH cells from primary bone lesions. Accordingly, complete resection followed by irradiation might be the most effective strategy with regard to complete control of the primary focus. Karpathiou et al recently reported a case of development of isolated pulmonary LCH followed by spontaneous regression with smoking cessation alone, 4 years after spontaneous regression of solitary bone LCH in an adult smoker (18). Thus, the primary site of disease remains in doubt, because pulmonary and bone lesions of LCH have also been reported to spontaneously resolve after smoking cessation alone (19).

Based on the experience of the treatment of pediatric patients with multisystem LCH, the lungs are considered as one of the “risk organs” (2). However, recent studies suggest that pulmonary involvement without involving other “risk organs” does not appear to be an unfavorable prognostic factor even in children with multisystem pulmonary LCH (20, 21). Pulmonary LCH with bone involvement may represent another entity despite the multisystem disease, which possibly has a good prognosis with minimal medical intervention (19). In conclusion, close observation with the maintenance of smoking reduction would be an appropriate treatment strategy in the present case to achieve a favorable outcome. Further studies of accumulated clinical features are needed to elucidate optimal management choices of multisystem pulmonary LCH and its pathogenesis.

The authors state that they have no Conflict of Interest (COI).

References


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