SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 244-248

The many faces of Pulmonary Langerhans Cell Histiocytosis

A. Biswas[1], M. Donahoe[2]

[1]Department of Internal Medicine University of Pittsburgh Medical Center East; [2]Associate Professor of Medicine, Director, Medical Intensive Care, University Of Pittsburgh

Abstract. Langerhans Cell Histiocytosis is a rare disease with variable presentation and prognosis in adults and in children. Histiocytosis of the ocular choroidal tissue has never been reported before in adults. We present two cases, one with choroidal involvement with asymptomatic nodulo-cystic changes in the lungs and another case with advanced single organ pulmonary involvement. We discuss the various treatment modalities and highlight the lack of adequate guidelines to treat adults. Most of the current guidelines are based on evidence derived from pediatric literature. We would also like to draw attention to the asymptomatic nature of the lung involvement and suggest that imaging of the lung be obtained in all cases of Langerhans Cell Histiocytosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 244-248)*

Key words: Pulmonary Langerhans Cell Histiocytosis, Lung Cysts, Lung Nodules, Choroidal tumor

Introduction

Pulmonary Langerhans Cell Histiocytosis (PLCH) is a predominantly cystic lung disease characterized by Langerhans Cell (LC) proliferation throughout the lung parenchyma. Recent studies point towards the role of a clonal proliferative process in a section of patients with PLCH after the detection of BRAF V600E oncogene mutations in those patients. The discovery has opened up an opportunity to use molecular targeted therapy in the treatment of PLCH (1).

Received: 10 December 2013
Accepted: 28 April 2014
Abhishek Biswas, MD
Department of Internal Medicine,
UPMC East
2775 Mosside Boulevard
Monroeville, PA-15146
Email: biswasa2@upmc.edu
Phone: (412) 706-0449
Fax: 412-357-3641

The pattern of organ involvement differs in children and adults. In children it is mostly a disease involving multiple systems with lung being involved in some cases. Isolated pulmonary involvement is quite uncommon in children. Isolated pulmonary disease is more common than MS-LCH (Multisystem-LCH) in adults and the lungs are the most common isolated organ involved. An improved understanding of the patho-physiology of the disease has resulted in the use of novel drugs for its treatment but there is yet no consensus about its standardized management. Smoking cessation has been universally accepted to be essential although there are no randomized trials to see how effective they are compared to steroids. LCH is a strange disease with up to one fourth of patients showing spontaneous regression whether they stop smoking or not.

We aim to discuss the clinical course of two patients with PLCH and highlight the differences in response to standard therapy. We would also like to present this very unusual case of choroidal and pulmonary involvement as a part of MS-LCH.

Case Presentation:

Case 1

A 28 year old lady, an active smoker, presented with painful, progressive, loss of vision in her right eye of four days duration. Fundoscopic examination revealed a serous retinal detachment associated with a choroidal mass of the right eye (Figure 1) (2). Orbital MRI revealed an area of faint enhancement on post-contrast fat saturation images posterior to the right globe (Figure 2). A High Resolution chest CT scan (Figure 3) revealed upper lobe predominant nodular and cystic disease of both lungs along with evidence for cavitation in some of these nodules. The differential diagnosis included Pulmonary Langerhans Cell Histiocytosis (PLCH) malignancy, tuberculosis, disseminated fungal disease, and granulomatous disease. A trans-bronchial lung biopsy (TBBx) was inconclusive leading to a video-assisted thoracoscopic lung biopsy. The biopsy showed multifocal granulomas containing histiocytes and eosinophils. The hemosiderin-laden macrophages stained strongly positive for CD68 and S100, but were CD1A negative. In contrast, histiocytes with pale grooved nuclei stained positively for CD1A and S100 and weakly for CD68. These findings were consistent with a diagnosis of Pulmonary Langerhans Cell Histiocytosis (PLCH).

The patient was initiated on 60 milligrams of prednisone and strongly advised to stop smoking at the

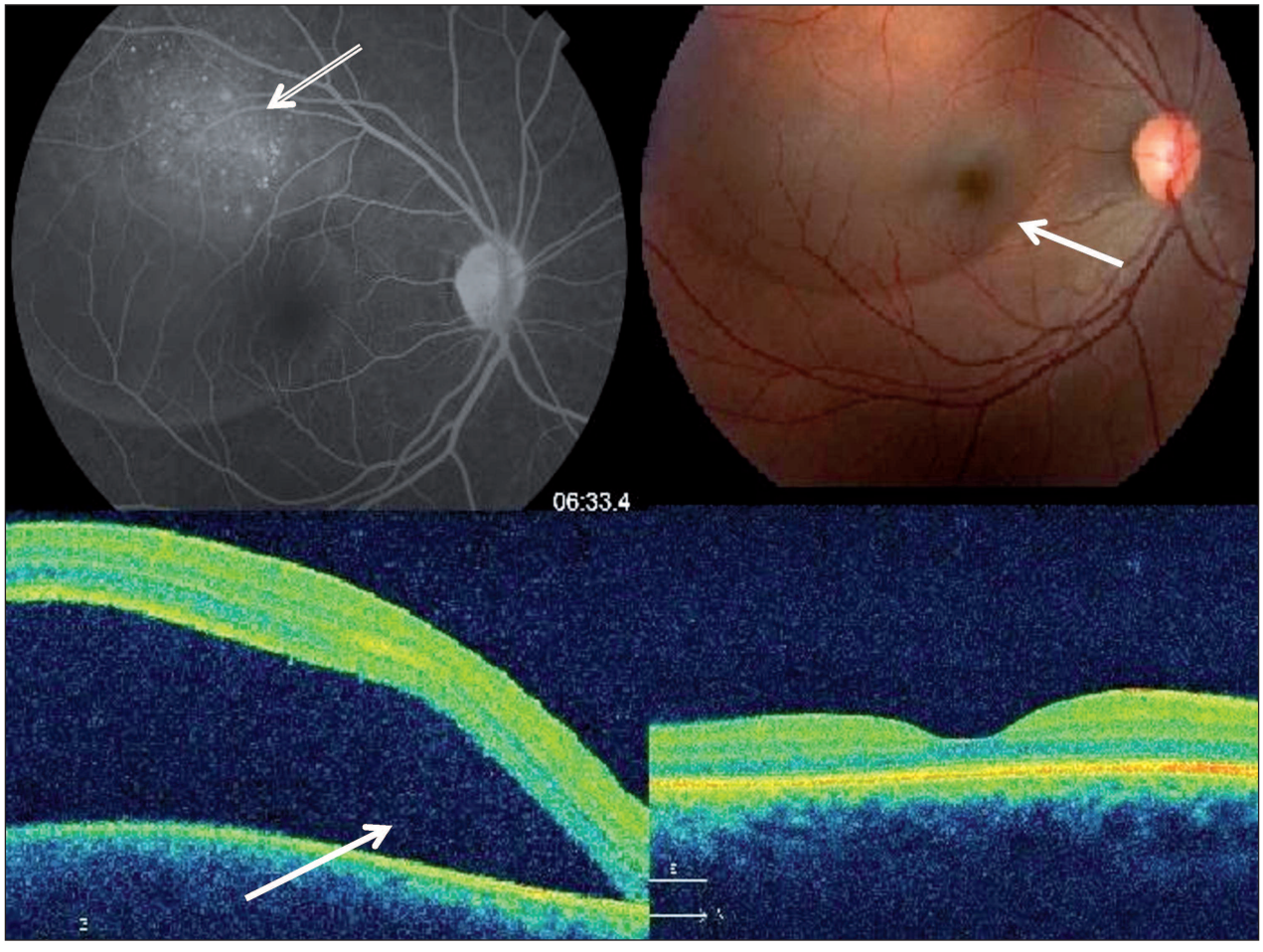

Fig. 1. Fundoscopic images of the retina and Fundus Flourescein Angiographic (FFA) images of the right eye. The arrow points towards the area (top left panel Figure 1) of mottled hyperflourescence in the arterio-venous phase of FFA. The arrow in the top right panel (Figure 1) points to the margin of a Serous Retinal detachment. Optical Coherence Tomography images of the right eye show initial retinal detachment followed by complete resolution of the detachment on follow-up scans after a month as demonstrated in the two images in the lower panel. The arrow points to the area of detachment in the left lower panel.

time of discharge which she immediately complied with. Follow up optical coherence tomography showed resolution of the retinal detachment with shrinkage of the choroidal mass (Figure 1) and normal visual acuity on exam. However, the CT scan of her chest demonstrated progressive cystic disease at the end of three months of steroid therapy (Figure 4). She was started on Vinblastine (6 mg/ m^2 weekly bolus intravenously for six weeks) and 80 milligrams of Prednisone (40 mg/m^2/day orally for four weeks which was then tapered over two weeks). Follow up CT scan at the end of six cycles of therapy showed significant resolution of the nodules and cysts. She tolerated the therapy quite well other than complaints of proximal weakness and some transient tingling in her hands and feet.

Case 2

A 58 year old male with an extensive smoking history presented with shortness of breath along with a productive cough. He endorsed a history of weight loss, anorexia, productive cough, chills and night sweats for two months. Initial chest films showed bilateral nodular interstitial shadows and a cavitary lesion in the right upper lobe. A contrast enhanced CT chest demonstrated solid nodular opacities with ground glass changes in a few that were randomly distributed in both the lungs along with a 3.7 cm cavitary lesion in the upper lobe of the right lungs (Left upper and lower panels in Figure 5). He was started on antibiotics for possible necrotizing pneumonia to which he responded promptly. A trans-bronchial biopsy (TBBx) was obtained which revealed peri-bronchial granulomas with Langer-

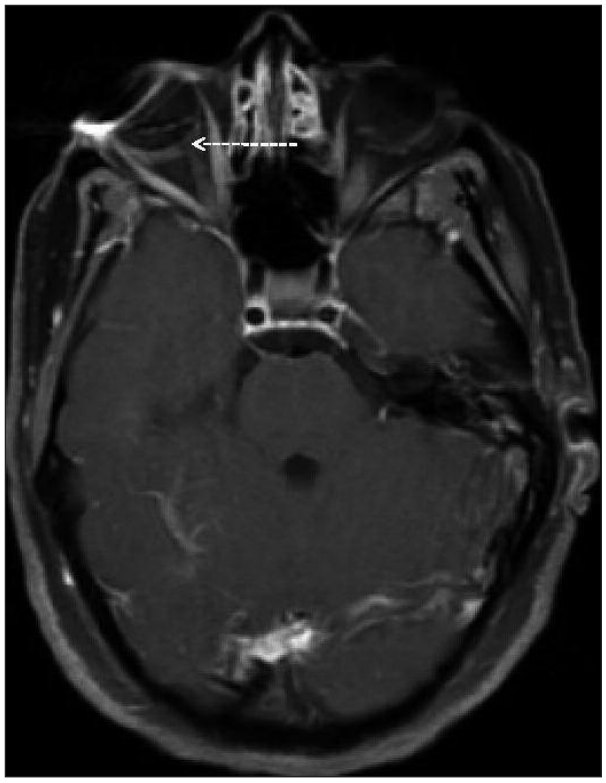

Fig. 2. MRI with contrast of the brain shows retro-bulbar enhancement at the posterior part of the (arrow) of the right globe.

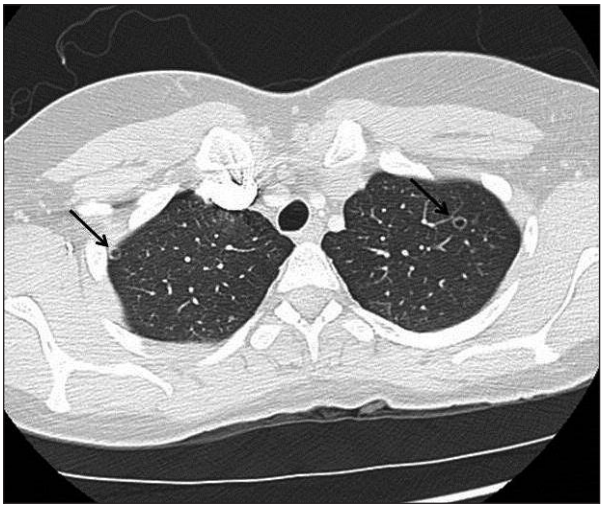

Fig. 3. CT scan of the lung showing bilateral small nodulo-cystic changes. Black arrows point towards the two largest cysts.

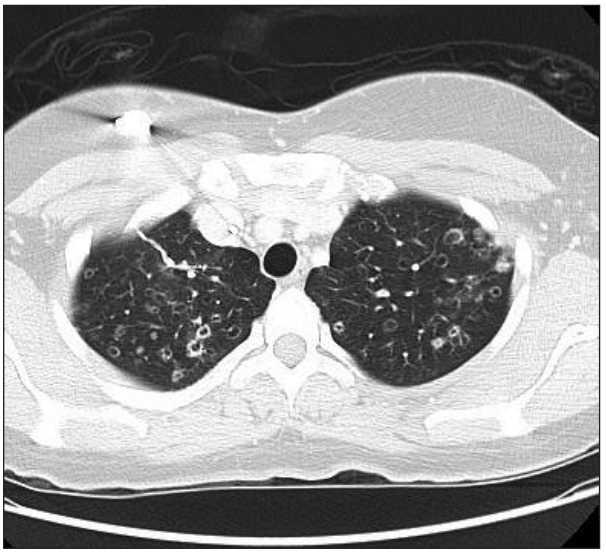

Fig. 4. A follow up CT scan of the same patient demonstrates more prominent nodulo-cystic changes bilaterally at the end of three months of therapy with high dose on corticosteroids.

hans cells that were CD68+/S100+/CD1a+ which was diagnostic of PLCH. He was adviced to stop smoking which he immediately complied with. On evaluation after three months he was noted to have a drop in his DLCO from 58% to 51% predicted. Imaging at this time did not reveal any improvement in the number of lung cysts and ground glass changes and he was started on Prednisone at 40mg/day. A follow up CT scan after one month demonstrated significant resolution of the nodules (Right upper and lower panels in Figure 5). He currently continues to lead an active life.

Discussion

Effective therapy for PLCH is a controversial subject with multiple facets that need further clarification. Most treatment guidelines for adult PLCH are derived from pediatric literature; however, these are regarded as distinct diseases. Unlike pediatric patients, where the lungs are not regarded as risk organs, survival in adults with PLCH is worse than in those with MS-LCH (3, 4, 5).

There is a lack of guidelines for appropriate treatment of adult PLCH. Smoking cessation is a time-honored first step of treatment, but a recent

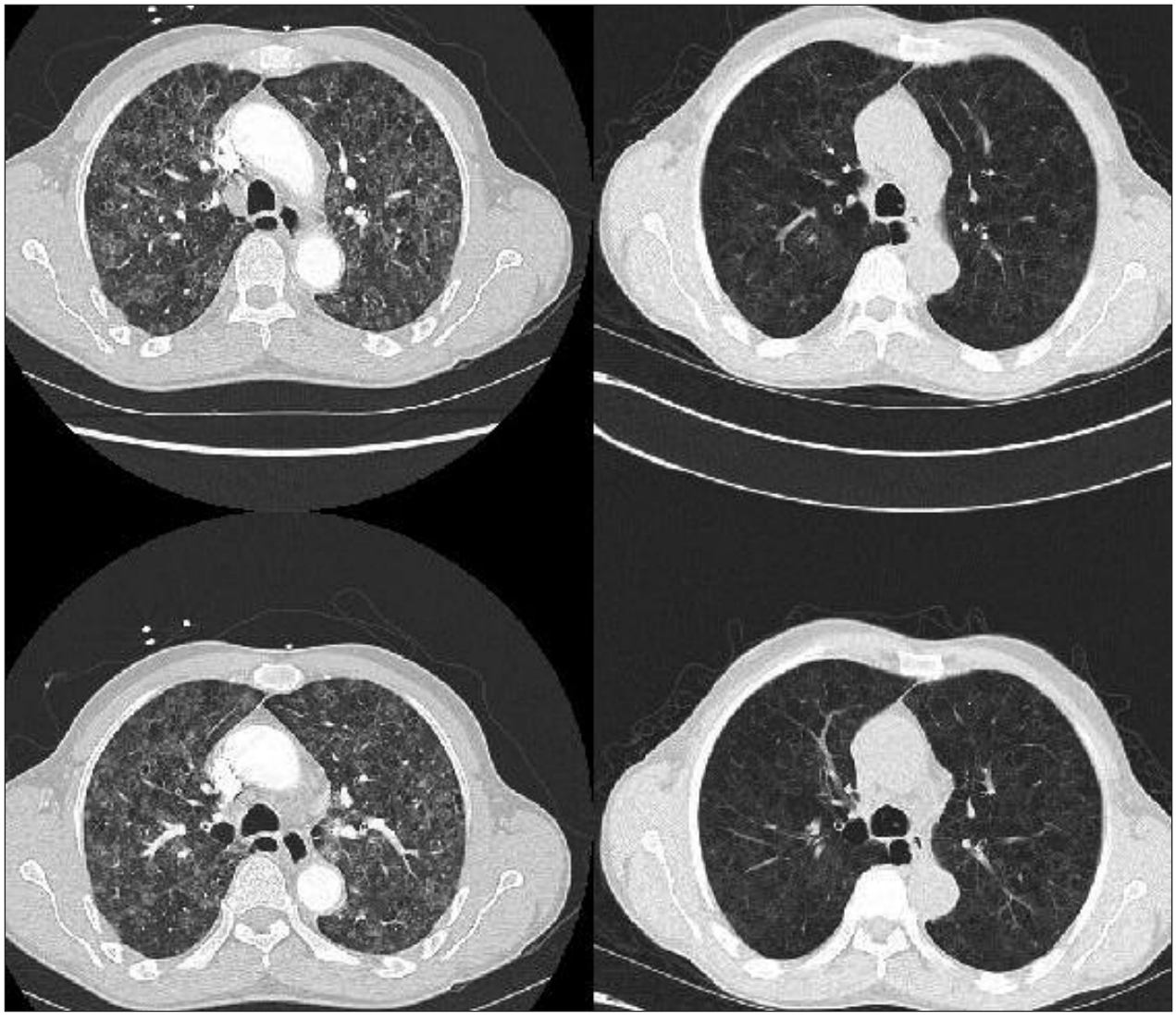

Fig. 5. CT scan of the chest demonstrating resolution of extensive nodulo-cystic changes with corticosteroid treatment in case of second patient. The cavitary lesion in the upper lobe of the right lung is not visible on these scans.

prospective study demonstrated statistically non-significant improvement in radiological findings between quitters and non-quitters (6). In general, corticosteroids are regarded as the initial pharmacological agent of choice. Schonfeld et al reported no progression of disease in 36 patients treated with steroids, with 85% of those patients showing positive response (7). One of the largest disease registries has shown disease free survival rates in 80% of PLCH patients treated with prednisone (8). Among other agents, a combination of Vinblastine and Prednisone has been used with varying response rates (60-90%) in pediatric patients with MS-LCH. However, this combination has only been used in the management of severe and refractory pulmonary disease in adults and no evidence exist to indicate their usefulness in the primary treatment of isolated PLCH. Cladribine can also be considered for management of refractory PLCH. A phase II trial in 13 patients with LCH, six of whom had pulmonary involvement, demonstrated a complete response rate of 50% (9).

Unfortunately, no study has ever compared any two treatment strategies for adults. The LCH AI trial was initiated with Vinblastine and Prednisone in adults but discontinued due to the 75% incidence of neurotoxicity from Vinblastine (10).

Identifying the agent of choice in patients who need aggressive therapy beyond corticosteroids remains unclear. Chemotherapeutic agents are currently reserved for those with severe risk organ involvement (11), severe constitutional symptoms and extra-pulmonary disease.

Patient 1 (MS-LCH) was treated with Vinblastine and Prednisone and demonstrated prompt clinic-radiological improvement after initially failing to improve with Prednisone alone. The disparity in the response of her disease with corticosteroids may indicate that pulmonary disease is more refractory to treatment than extra-pulmonary disease in adults. This might account for the worse 5 years survival rate in adults with PLCH (87.8%) compared to those with MS-LCH (91.7%) (3).

On the other hand, patient 2 had an excellent response to corticosteroids, reflecting their role as first line agents for isolated PLCH.

It was also noted that TBBx (sensitivity of 10-40%) (12-13) provided adequate samples for diagnosis in patient 2. It is conceivable that patients with pronounced nodulo-cystic changes on CT scan might not need a VATS assisted lung biopsy and can be diagnosed with adequately performed TBBx.

This case series both highlights the common protocols used in the management of PLCH and underscores the lack of convincing evidence supporting their use. In the absence of well conducted, randomized clinical trials, clinicians are left to base treatment on perceived risk to benefit ratios.

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