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Case report

Erdheim Chester Disease treated successfully with cladribine

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ABSTRACT

A 61-year-old previously healthy male with a history of progressive fatigue, lower extremity edema, and dyspnea for 4 months was hospitalized with pericardial and pleural effusions (Figure 1A, B). Lung, pleural, and pericardial biopsies were consistent with Erdheim-Chester disease. He was treated with systemic steroids, and ultimately tried on PEG-interferon. He deteriorated clinically and the disease progressed to include CNS manifestations. Ultimately he was treated with Cladribine, at a dose 0.014 mg/kg on day 1, followed by 0.09 mg/kg/day = 6.4 mg IV for 6 additional days. He received 2 further cycles of 0.14 mg kg/day for 7 days (1 month apart). After 3 cycles he improved significantly both clinically and radiographically. Six months post-treatment objective testing showed improvement in cardiac, neurologic, and pulmonary disease.

Erdheim Chester Disease (ECD) is a rare non Langerhans cell histiocytosis. Only several hundred cases have been reported in the literature. Treatment for ECD is reserved for those with symptomatic disease, asymptomatic CNS involvement, or evidence of organ dysfunction. There is no standard treatment regimen: Current options include corticosteroids, Interferon alpha (IFN), systemic chemotherapy, and radiation therapy. The occurrence of the V600EBRAF mutation in about 50% of patients can make these patients amenable to targeted therapy with BRAF kinase inhibitors (e.g. Vemurafenib). More recently the presence of N/KRAS, and PIK3CA mutations have provided further rational for targeted therapies. The cytokine profile in patients with ECD suggests monocyte activation cladribine, a purine analogue toxic to monocytes, has also been studied as a treatment for ECD, especially in patients who test negative for the BRAF mutation.

1. Introduction

Erdheim Chester Disease (ECD) is a rare non-Langerhans cell histiocytosis. Only several hundred cases have been reported in the literature since it was first described in 1930 [1]. It has been diagnosed in all age groups, more commonly in males between the 5th and 7th decades of life [2]. While the pathophysiology is not completely understood recent data shows that at least 50% of cases harbor a BRAF mutation and that other cases may show ERK activation [1,3]. Treatment largely depends on the organ system (s) involved and the extent of organ damage [4]. Recent advances in mutation analysis have identified possible targeted therapies for treatment [5]. Cladribine is FDA approved for hairy cell leukemia and has several other off-label uses, including Langerhans cell Histiocytosis (LCH) and other lymphoproliferative disorders [6]. While it has been used in ECD with some promise reports of its use are scant [1,7].

2. Case

A 61-year-old previously healthy male with a history of progressive fatigue, lower extremity edema, and dyspnea for 4 months was hospitalized at an outside facility and diagnosed with a pericardial effusion and bilateral pleural effusions (Fig. 1A and B). Lung, pericardial, and pleural biopsies were consistent with Erdheim-Chester disease (ECD) (Figs. 3 and 4). Treatment with prednisone

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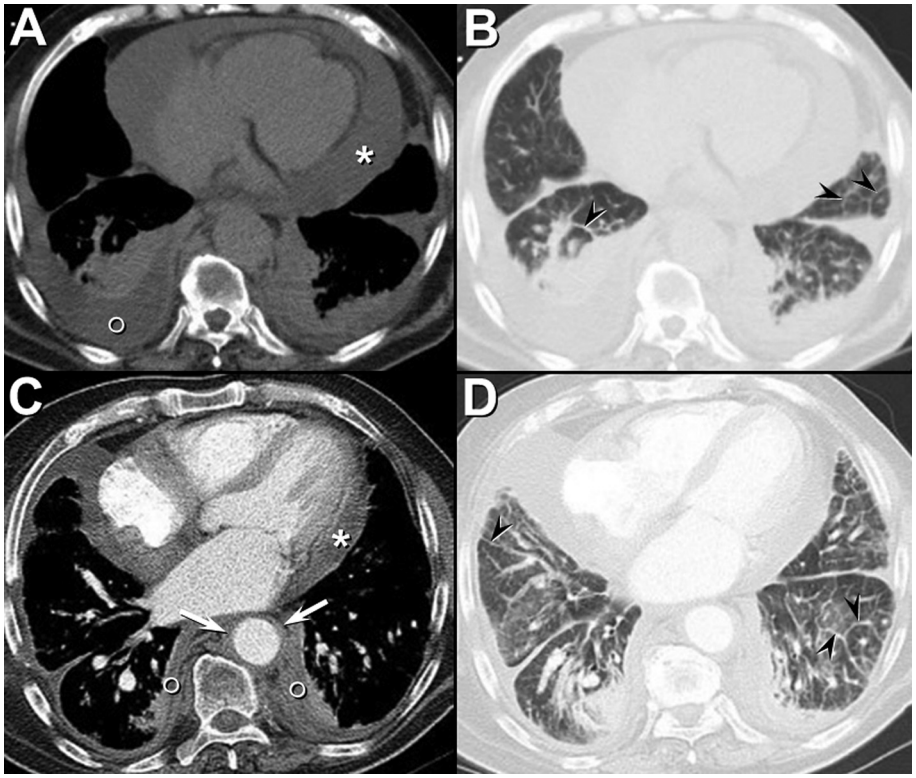

Fig. 1. Unenhanced thoracic CT prior to therapy initiation displayed in soft tissue (A) and lung (B) windows shows bilateral pleural effusions (○), a moderate-sized pericardial effusion (*), and basal interlobular septal thickening (arrowheads). Enhanced thoracic CT displayed in soft tissue (C and lung (D) windows, performed approximately one year following initiation of corticosteroid therapy, shows reduction in bilateral pleural effusions (○) and pericardial effusion (*), but with increasing interlobular septal thickening (arrowheads). Perivascular soft tissue infiltration surrounding the descending thoracic aorta (arrows) is evident.

at 40 mg per day was initiated with significant clinical improvement allowing the patient to be discharged with supplemental oxygen via nasal cannula.

He was referred to our institution 4 months later on 40 mg of prednisone daily, attempts to taper prednisone had failed. He complained of continued fatigue, progressive functional decline, shortness of breath, and was dependent on supplemental oxygen. An echocardiogram revealed cardiac muscle hypertrophy, and elevated filling pressures in addition to small pericardial effusions and adhesions without constrictive hemodynamics. Repeat thoracic computed tomography (CT) (Fig. 1C and D) showed bilateral pleural effusions, pericardial effusions, and diffuse interlobular septal thickening. Pulmonary function tests (PFTs) showed a severe restrictive defect, forced vital capacity (FVC) of 46% and diffusion capacity for carbon monoxide (DLCO) 55%.

The patient's prednisone dose was increased to 60 mg/day resulting in some improvement in symptoms; a second attempt to taper prednisone over the course of a few months was unsuccessful. While the abnormalities on thoracic CT remained stable (Fig. 2A and B), PFTs revealed worsening restriction and worsening of diffusion capacity (FVC decreased from 46% to 34%, and DCLO 55% to 36%). The tumor was negative for the BRAF mutation, eliminating consideration of Vemurafenib (BRAF kinase inhibitor). The patient was started on PEG interferon (IFN) (100/80 mcg subcutaneously weekly), with reduced oxygen requirements and improvement in overall strength after 10 weeks of therapy without any undue toxicity. The prednisone dose was tapered to 9 mg per day and his pulmonary function testing had improved. This clinical improvement was transient and the patient developed worsening symptoms after just a few months of therapy. Furthermore the patient developed central nervous system (CNS) disease marked by progressive neurological symptoms, including cognitive decline and gait abnormalities. An MRI of the brain revealed T2 signal abnormalities in the cerebellum extending to the peduncles and 4th ventricle, as well as in the pons and posterior midbrain. Cladribine was started because of the neurologic disease progression, at a dose of 0.014 mg/kg on day 1, followed by 0.09 mg/kg/day = 6.4 mg IV for 6 additional days [2,7]. He received 2 further cycles of 0.14 mg kg/day for 7 days (1 month apart). After 3 cycles he improved significantly both clinically and radiographically.

Six months post-treatment, objective testing showed improvement in neurologic, cardiac, and pulmonary disease. The echocardiogram showed significant improvement with stabilized systolic function with an EF of 50%, a significant improvement in diastolic function, and a large improvement in right ventricular systolic pressure. MRI brain revealed improved lesions in the posterior fossa previously described. PFTs and findings on CT chest also improved. (Fig. 2C and D).

3. Discussion

Non-Langerhans histiocytoses are derived from the monocyte-macrophage lineage. Clinical manifestations vary, and can involve various organ systems [4,8], but the most common clinical presentations are bone pain, neurological features, diabetes insipidus, and constitutional symptoms [8]. The long bones, heart, lungs, central nervous system (CNS), skin, pituitary gland and orbits are the most commonly involved [13]. The disease course can be relatively benign with spontaneous remission, or rapidly progressive and fatal. Prognosis is largely dependent on the number and extent of organs involved, however CNS involvement is an independent predictor of survival [8,9].