Erdheim Chester Disease treated successfully with cladribine

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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 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.

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 [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. While it has been used in ECD with some promise reports of its use are scant [6–8].

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 (Figure 1A and B). Lung, pleural, and pericardial biopsies were consistent with Erdheim-Chester disease (ECD) (Figures 3 and 4). Treatment with prednisone...
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) [9]. 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. 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 [10,11]. 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 histiocytes are derived from the monocyte-macrophage lineage. Clinical manifestations vary, and can involve various organ systems [4], but the most common clinical presentations are bone pain, neurologic features, diabetes insipidus, and constitutional symptoms [12]. 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 [14], however CNS involvement is an independent predictor of survival [15].
Treatment for ECD is reserved for those with symptomatic disease, asymptomatic CNS involvement, or evidence of organ dysfunction. While close monitoring has been recommended for those without CNS involvement and no symptoms, the paucity of data limits these recommendations [1]. There is no standard treatment regimen: Current options include corticosteroids, Interferon alpha (IFN), systemic chemotherapy, and radiation therapy [1]. ECD is thought to be a clonal disorder originating from the monocytic myeloid lineage. The driving molecules appear to involve the BRAF and NRAS signal pathways. The occurrence of the V600EBRAF mutation in about 50% of patients can make these patients amenable to targeted therapy with BRAF kinase inhibitors (Vemurafenib) [16]. In addition, other mutations such as N/KRAS, and PIK3CA have provided further rational for targeted therapies [5].

Systemic chemotherapy regimens have been studied in other histiocytic disorders, such as LCH. Such therapies are considered for patients who fail to respond to IFN or who develop intolerable side effects. The most commonly used regimen is a 24-week treatment consisting of vinblastine, etoposide, prednisone and 6-mercaptopurine. The rationale behind these agents is lacking and their use is largely empirical as these drugs were the only ones available in the chemotherapeutic armamentarium when treatment for this disease was first reported. More recent literature suggests that in addition to BRAF, there are other mutations that can be amenable to targeted therapies; such as N/KRAS, and PIK3CA.

**Fig. 2.** Repeat enhanced thoracic CT prior to initiation of cladribine therapy, but following PEG interferon treatment, displayed in soft tissue (A) and lung (B) windows shows resolution of pericardial fluid but with development of pericardial and cardiac soft tissue infiltration (*); similarly, pleural liquid has resolved, but extensive pleural thickening (○) has developed. Interlobular septal thickening (arrowheads) with patchy bilateral increased lung opacity and periaortic soft tissue infiltration (arrows) persist. Enhanced thoracic CT displayed in soft tissue (C) and lung (D) windows 4 months following completion of 3 cycles of cladribine therapy shows persistent but decreased bilateral medial basal pleural thickening (○) with persistent but slightly less pronounced bilateral interlobular septal thickening (arrowheads) and overall improved in bilateral lung opacity compared to (B).

**Fig. 3.** Wedge biopsy of lung, including pleura. There is both pleural and interlobular septal thickening (left panel, hematoxylin-eosin, x4), as a result of an accumulation of foamy macrophages (right panel, hematoxylin-eosin, x400). These macrophages expressed CD68, and Factor XIIIa, but not CD1a, as is characteristic of Erdheim-Chester disease.
is successful regardless of previous treatment regimens for adults with ECD. The disease in our patient had failed to exhibit sustained responses to several treatment regimens. After just 3 cycles of cladribine the patient had significant improvement which was sustained at 15 months of followup. This response appears to come with a relatively favorable toxicity profile. Cladribine therapy does confer long-term T cell depletion and, given its incorporation into DNA, can be potentially mutagenic; thus only patients who are symptomatic or have CNS involvement should receive this therapy, and subsequently should be monitored closely for adverse effects.

Conflict of interest

None.

Funding source

None.

References

[1] G. Rigatelli, A. Zamboni, Global endovascular or surgical treatment: a challenging case of combined coronary artery, abdominal aorta and iliac arteries inflammatory aneurysmal disease, J. Invasive Cardiol. 16 (10) (2004) 585–586 discussion 586.
[2] C. Rigatelli, M. Gemelli, G. Franco, A. Mesini, Unusual combination of coronary artery, abdominal aortic and iliac artery inflammatory aneurysmal disease, Int. J. Cardiol. 96 (1) (2004) 105–107.
[3] B.N. Potkin, J.M. Hoeg, W.E. Conner, G. Salen, A.A. Quyyumi, J.E. Brush Jr., et al., Aneurysmal coronary artery disease in cerebrotendinous xanthomatosis, Am. J. Cardiol. 61 (13) (1988) 1150–1152.
[4] J. Haroche, Z. Amoura, B. Wechsler, C. Veyssier-Belot, F. Charlotte, J.C. Piette, Erdheim-Chester disease, Presse Med. 36 (11 Pt 2) (2007) 1663–1668.
[5] F.J. Emile, E.L. Diamond, Z. Helias-Rodzewicz, F. Cohen-Aubart, F. Charlotte, D.M. Hyman, et al., Recurrent RAS and PIK3CA mutations in Erdheim-Chester disease, Blood 124 (19) (2014) 3016–3019.
[6] H. Ribeiro, P. Sousa, H. Carvalho, R. Margato, C. Pinto, P. Magalhaes, et al., Severe aneurysmal coronary artery disease in a patient with ulcerative colitis, Rev. Port. Cardiol. 31 (7–8) (2012) 525–526.
[7] R. Gorla, A. Macchi, I. Franzoni, P. Spagnolo, A. Margonato, ‘clover’ coronary artery: role of coronary computed tomography to indicate optimal treatment in aneurysmal coronary artery disease, J. Cardiovasc. Med. Hagerst. 14 (1) (2013) 76–77.
[8] O.M. Shapira, R.J. Shemin, Aneurysmal coronary artery disease. Atherosclerotic coronary artery ectasia or adult mucocutaneous lymph node syndrome (Kawasaki’s disease)? Chest 111 (3) (1997) 796–799.
[9] M. Ochiai, T. Yamaguchi, J. Taguchi, M. Ohno, H. Yoshimura, M. Kushida, et al., Angioplasty of stenoses adjacent to aneurysmal coronary artery disease, Jpn. Heart J. 31 (6) (1990) 749–757.
[10] C. Myra, L. Sloper, P.J. Tighe, R.S. McIntosh, S.E. Stevens, R.H. Gregson, et al., Treatment of Erdheim-Chester disease with cladribine: a rational approach, Br. J. Ophthalmol. 88 (6) (2004) 844–847.
[11] B.D. Mazor, M. Manevich-Mazor, Y. Shoenfeld, Erdheim-Chester disease: a comprehensive review of the literature, Orphanet J. Rare Dis. 8 (2013) 137.
[12] S. Felis, W. Deste, A. Ragusa, D. Giannotta, V. Casaccio, G. Barbagallo, et al., Coronary artery ectasia or adult mucocutaneous lymph node syndrome (Kawasaki’s disease)? Ital. Heart J. 4 (9) (2003) 633–637.
[13] T. Bessot, R. Battellini, J.F. Gummert, F.W. Mohr, Aneurysmal coronary artery disease of the right coronary artery, Eur. J. Cardiotherac. Surg. 24 (4) (2003) 641.
[14] N. Lamblin, C. Bauters, X. Hermant, J.M. Lablanche, N. Helbecque, P. Amouyel, Polymorphisms in the promoter regions of MMP-2, MMP-3, MMP-9 and MMP-12 genes as determinants of aneurysmal coronary artery disease, J. Am. Coll. Cardiol. 40 (1) (2002) 43–48.
[15] J.S. Jurgensen, M. Schlegl, J. Hug, Severe aneurysmal coronary artery disease, Heart 86 (4) (2001) 404.
[16] V.P. Demopoulos, C.D. Olympios, C.N. Fakiolas, E.G. Pissimissis, N.M. Economides, E. Adamopoulou, et al., The natural history of aneurysmal coronary artery disease, Heart 78 (2) (1997) 136–141.