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CASE REPORT

A Rare Case of Erdheim–Chester Disease with Pseudoprogression in the CNS

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Abstract: Erdheim-Chester Disease (ECD) is a rare histiocytic neoplasm characterized by multi-organ tissue infiltration by histiocytes. Clinical presentation and course can be heterogeneous, ranging from localized and asymptomatic bone lesions to a multisystem disease involving skin, cardiac, pulmonary, retroperitoneum, lymph node and central nervous system (CNS) with significant morbidity and mortality. Herein, we describe a rare case of a 61-year-old female patient with ECD with primarily brain and bone involvement who developed "progressive disease" in the CNS after 3 cycles of cladribine. The patient elected to forego any further treatment based on her clinical stability despite progressive disease imaging findings. Subsequent imaging while off treatment demonstrated marked interval improvement in the previously patchy areas of involvement and the patient has continued to have clinical stability 4 years after stopping therapy. The patient was deemed to have experienced pseudoprogression. Pseudoprogression of ECD has not been reported in the literature, and it may be associated with localized inflammatory cytokine release in response to treatment. The possibility of pseudoprogression needs to be considered in evaluating therapeutic response in ECD patients.

Keywords: Erdheim–Chester, pseudoprogression, CNS disease, cladribine

Introduction

Erdheim–Chester Disease (ECD) is a rare histiocytic neoplasm characterized by multi-organ tissue infiltration by clonal histiocytes.[1] Clinical presentation and course can be heterogenous ranging from localized and asymptomatic bone lesions to a multisystem disease with significant morbidity and mortality.[2] The diagnosis of ECD is challenging and requires a combination of radiographic and pathological findings.[3] A defining clinical feature of ECD is symmetric osteosclerosis of the metadiaphyses of the lower-extremity bones on positron emission tomography (PET) scan. Approximately 1/3 of patients will develop retroperitoneal fibrosis, especially around the kidneys and ureters and 25–50% of patients will present with central nervous system (CNS) involvement – most often cerebellar involvement. Histopathology is characterized by infiltration of tissues by foamy mononucleated histiocytes with small nuclei. A few multinucleated histiocytes or Touton cells are also frequently observed. Fibrosis is present in most cases as well as reactive lymphocytes, plasma cells and neutrophils.[4,5] On immunohistochemistry, histiocytes are positive for CD68, CD163, factor XIIIa and fascin and negative for CD1a and CD207.[3] More recently, molecular testing has become essential since >80% of patients harbor activating somatic mutations or fusions in the genes of the MAPK-ERK or the PI3K-AKT pathway, including BRAFV600E mutation.[3,6] Due to the rarity of ECD as well as its heterogeneous presentation, ECD patients may see multiple providers and undergo several biopsies that usually lead to a delayed diagnosis.[3] Most patients with ECD require systemic treatment at diagnosis except for asymptomatic, non-vital single organ involvement or minimally symptomatic disease that can be monitored.[3] Treatment options include targeted therapies with BRAF-inhibitors such as vemurafenib, dabrafenib and encorafenib, MEK-inhibitors such as cobimetinib, trametinib, binimetinib, selumetinib, mTOR inhibitors, interferon-α (INF-α), cytokine-directed therapy and cytotoxic chemotherapy including cladribine, cyclophosphamide, cytarabine, vinblastine, high-dose methotrexate and even autologous bone marrow stem cell transplant.[7–12] Unusual

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response patterns such as pseudoprogression have been described in several patients mostly those that are treated with immunotherapy.[13] Pseudoprogression is a phenomenon where treatment with chemotherapy, radiotherapy and/or immunotherapy provokes increased contrast agent uptake and seemingly enlargement of residual tumor or the appearance of new lesions mimicking tumor progression, but it is mostly attributed to inflammation rather than to true progression[14,15] Herein, we describe the first case in the literature of pseudoprogression in a patient diagnosed with ECD with CNS involvement after being treated with cladribine.

Case Presentation

A 61-year-old female with no significant past medical history developed symptoms of fatigue, increased urination, vertigo, and imbalance. Four years later, her imbalance, vertigo, and dizziness significantly worsened, and her symptoms were attributed to unconfirmed carbon monoxide poisoning. Due to progressive symptoms, an MRI of the brain with contrast was obtained, which revealed diffuse increased T2/FLAIR signals surrounding the fourth ventricle involving the dorsal pons, middle cerebral peduncles, inferior aspect of the midbrain. The cerebellum was found to be diminutive, with atrophic superior cerebellar folia and mild atrophy of the superior cerebellar peduncles with significant white matter loss. A brain biopsy did not yield any diagnostic findings. She underwent repeated MRIs of the brain every 3–6 months for 2 years thereafter which continued to demonstrate unchanging lesions in the brainstem and cerebellum with new lesions in the pituitary gland. The patient's primary complaint during this time remained excessive fatigue, dizziness and she also developed diplopia. There was a concern for a demyelinating process and CLIPPERS disease, so she was started on high-dose steroids with a prednisone taper without significant improvement of her symptoms. Patient was referred to our facility for further evaluation. Neuromyelitis optica (NMO/AQP4) antibodies and myelin oligodendrocyte glycoprotein (MOG) IgG antibodies were negative, in addition, a complete paraneoplastic panel, oligoclonal bands and infectious panel were also unremarkable. Repeat suboccipital stereotactic biopsy of the brain was non-diagnostic.

The patient's symptoms persisted for a year without a clear diagnosis. Although the patient did not have significant bone or joint pain, but due to brain MRI findings concerning for possible Erdheim Chester Disease a nuclear medicine bone scan was performed and revealed multiple osteosclerotic lesions involving primarily the long bones of the lower extremities. She underwent biopsy of the right tibia, which showed foamy macrophages on histological examination. Immunohistochemistry staining was negative for BRAF mutation (Figure 1). Cell-free DNA was tested for BRAFV600E mutation was also negative. An electrocardiogram and echocardiogram did not show evidence of cardiac involvement and a bone marrow biopsy with next-generation sequencing for myeloid neoplasms was also normal. Based on clinical, radiographic, and pathologic findings, the patient was diagnosed with BRAFV600E-negative Erdheim-Chester Disease with CNS involvement, diabetes insipidus, and widespread involvement of the long bones. Due to the extent of CNS involvement and clinical symptoms, it was decided to use a therapeutic agent with excellent CNS penetration. Thus, the patient was initiated on cladribine 5 mg/m^2 for days 1–5 every 28 days for 3 cycles. Following her third cycle, an MRI of the brain was performed which demonstrated disease progression with increased enhancement and T2 signaling within the brainstem and cerebellum (Figure 2). Whole-body PET scan noted persistent uptake in the long bones in keeping with active disease as well as interval increase in uptake in the C6 region of the cervical spine. There were, however, no new lesions identified, and the patient's symptoms improved and were stable.

She underwent a repeat bone biopsy of the distal left femur, which confirmed patchy infiltrates of foamy histiocytes. IHC staining of CD68 (KP1) highlighted histiocytic infiltrates, compatible once again with Erdheim-Chester Disease. The patient elected to forego any further treatment in the setting of worsening imaging findings of disease progression due to clinical improvement of her symptoms. Three months later, another MRI of the brain was carried out while off therapy and demonstrated marked interval improvement in the previously patchy areas of involvement in the brainstem, cerebellum, and C6 region, which was unexpected. The patient was deemed to have experienced pseudoprogression in the CNS and C6 vertebrae following her three cycles of cladribine. Her subsequent scans demonstrated improvement without any further therapeutic intervention. Furthermore, the patient's symptoms seemed to have improved with mild generalized fatigue being her only current complaint. Further treatment options were discussed with the patient, including monitoring, radiation, and/or systemic therapy with CNS penetrating agents including high-dose methotrexate, cytarabine and cobimetinib but since the patient's disease process only seemed to be slowly progressive while maintaining good

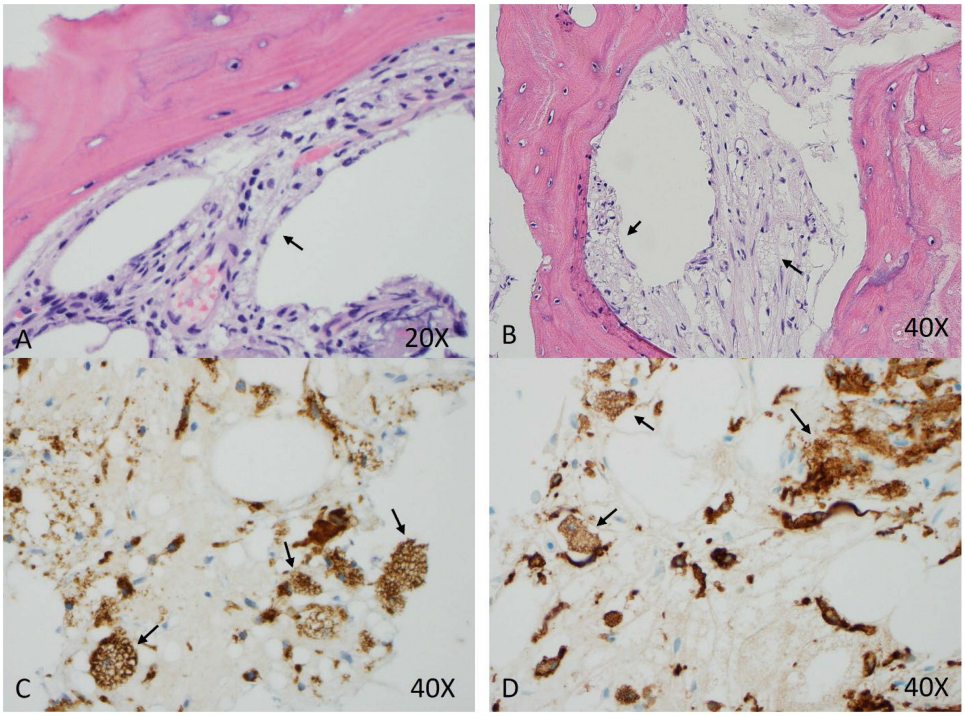

Figure 1 The biopsy of right tibia shows diffuse proliferation of foamy macrophages along the bone trabeculae ((**A**), Hematoxylin and Eosin 20X). A subsequent biopsy of left femur reveals the similar finding ((**B**), Hematoxylin and Eosin 40X). Immunohistochemistry studies show the foamy macrophages are positive for CD68 and CD163 ((**C** and **D**), 40X); and negative for S-100, CD1a, and BRAF V600F. Arrows in each image point to the clusters (**A** and **B**) and individual foamy macrophages (**C** and **D**).

functional status and quality of life, the decision was made to continue monitoring with surveillance MRI and PET scans every 6 months. The patient remains clinically stable 4 years after stopping therapy.

Discussion

Erdheim–Chester disease is a rare, non-Langerhans histiocytosis disease that has gained increasing recognition over the last two decades. CNS involvement is observed in 25–50% of the patients with gadolinium-enhancing lesions that can involve the cerebral hemispheres or the cerebellar tentorium.[16] Other organ system involvement can include skin, cardiac, pulmonary, retroperitoneum, lymph node and bone infiltration by foamy or lipid-laden histiocytes with admixed or surrounding fibrosis.[1] Some reports indicate that more than 80% of patients harbor activating somatic mutations or fusions in the genes of the MAPK-ERK or the PI3K-AKT pathway, specifically BRAFV600E mutation, which can be found in approximately 60% of patients.[3,6] Our patient did not harbor BRAFV600E or any other mutations in the MAP kinase proteins. Many different treatment options have been evaluated in Erdheim-Chester disease including targeted therapy based on mutational status such as BRAF-inhibitors or cytokine directed therapy and cytotoxic chemotherapy including cladribine, cyclophosphamide, cytarabine, vinblastine, high-dose methotrexate and even autologous bone marrow stem cell transplant.[7–12] Based on our patient's CNS dominant disease and neurological symptoms it was decided to start the patient on CNS-penetrating treatment with cladribine. Cladribine is a synthetic chlorinated deoxyadenosine analog which after several phosphorylation steps gets incorporated into cellular DNA, altering the double helix structure, and leading to a failure of DNA synthesis and repair. It is also involved in the inhibition of key enzymes in DNA and RNA synthesis including DNA polymerase and ribonucleotide reductase.[17] It is commonly used in the treatment of hairy cell leukemia, acute myeloid leukemia and several different types of lymphomas and histiocytic disorders. Cladribine can penetrate the intact blood–brain barrier, and it has been suggested that it may affect the recruitment of inflammatory cells and lymphocytes in the CNS in patients with multiple sclerosis.[17] There have been several case reports and case series published in the literature describing the successful treatment of Erdheim-Chester disease with cladribine.[18,19] Goyal et al performed a retrospective single institution review of 63 adult patients diagnosed

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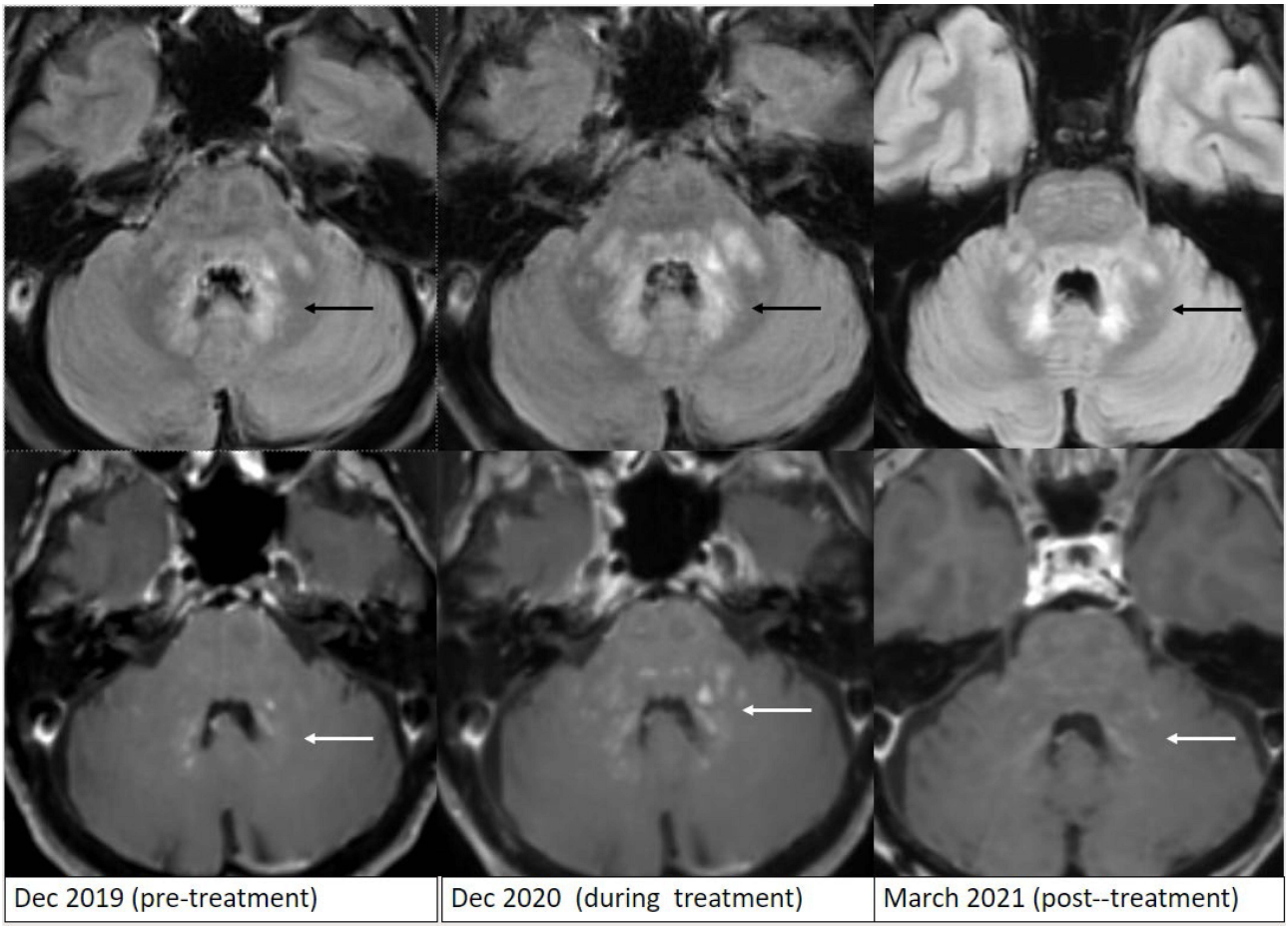

Figure 2 Multiple FLAIR images (top row) and post-contrast T1-weighted images (bottom row) in a 61 year old woman with Erdheim Chester disease obtained before, during and after treatment. Pseudoprogression of edema (black arrow) noted during treatment with associated increase in patchy enhancement (white arrows). Near complete resolution of enhancement and decreased edema noted in the follow up post-treatment MRI.

with EDC out of which 21 patients were treated with cladribine. The mean age at diagnosis was 54 years, and 67% of patients were male. Overall clinical response rate was 52% with 6% achieving a complete response (CR) and 46% a partial response (PR). Among patients who responded to cladribine, the median duration of response was 9 months (range 6–129 months). There was no description of pseudoprogression or other atypical responses to cladribine in their report.[20]

Interestingly, once our patient was started on treatment her neurological symptoms improved with only mild fatigue remaining. MRI of the brain after her third cycle showed "progression of disease" with increased signal and enhancement compared to the brain MRI prior to treatment (Figure 2). Therapy was held and a repeat brain MRI 3 months later showed an interval decrease in enhancement. Atypical response patterns to therapy have been recognized in neoplastic and inflammatory disorders, including pseudoprogression and hyperprogression.[21] Pseudoprogression is an unconventional phenomenon in which an initial increase in tumor size or uptake is observed or new lesions appear followed by a decrease in tumor burden.[14] This phenomenon was first described in brain tumors treated with temozolomide or radiation.[22] The mechanism of pseudoprogression has not been completely elucidated, but several hypotheses have been put forth including radiation-induced vascular changes that may lead to increased gadolinium enhancement, infiltration of immune cells, edema and necrosis.[22,23] The incidence of pseudoprogression varies widely ranging from 9% to 30% with its frequency increasing with the use of immunotherapy.[14,21] There are substantial ramifications for patients and clinicians when pseudoprogression is not identified such as premature discontinuation of an effective treatment.[15] Until now, there has not been a uniform identification standard for pseudoprogression, but it is crucial to correlate

findings with clinical symptoms. This is the first case reported in the literature describing pseudoprogression in a patient with ECD. We hypothesize that in this case pseudoprogression may be associated to localized cytokine release from histiocytic infiltrate secondary to cytotoxic activity by cladribine. Prior studies including the largest series reviewing the efficacy of cladribine in EDC have not explicitly mentioned pseudoprogression or other atypical responses, but this inflammatory phenomenon can complicate the interpretation of treatment efficacy, as initial imaging may suggest worsening disease despite clinical improvement or eventual radiologic response and cause premature discontinuation of an effective therapy.

In conclusion, pseudoprogression of ECD can develop during treatment. It is difficult to differentiate this phenomenon from true disease progression. Physicians who treat patients with ECD should consider the possibility of pseudoprogression and correlate radiological findings with clinical symptoms and consider close follow-up imaging to distinguish it from true progression of disease.

Limitations

There are many limitations in this case. This is a retrospective review of a single case, so our results cannot be generalizable. During the patient evaluation at progression of her symptoms there was no repeat brain biopsy since the initial biopsy was invasive and did not yield any diagnostic findings. At the time of her evaluation, there were no strict radiological response criteria to assess EDC lesions in the brain. Additional molecular evaluation may be helpful to determine therapy and assess for risk factors for pseudoprogression.

Ethics Statement

Institutional approval was not required to publish case details.

Written informed consent for publication of their details was obtained from the patient.

Disclosure

The author(s) report no conflicts of interest in this work.

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