A rare differential for sinusitis and visual loss

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ABSTRACT

Erdheim–Chester disease is a rare infiltrative histiocytic disorder with around 800 cases being reported worldwide. Patients most commonly present with skeletal pain, but the condition has been shown to affect multiple other organs. We describe a rare presentation in which the disease infiltrated the sinuses and affected an ex-RAF pilot's vision. After extensive investigation of the elusive diagnosis, repeating of a molecular test using polymerase chain reaction analysis allowed for identification of a mutation (BRAF V600) ultimately leading to the diagnosis of Erdheim–Chester disease.

KEYWORDS

Otolaryngology – Erdheim–Chester disease – Vision and hearing loss

Accepted 7 July 2019

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Background

Erdheim–Chester disease (ECD) is a very rare infiltrative histiocytic disorder that can affect multiple organ systems.¹ Around 800 cases have been reported worldwide to 2018. The first two cases and the pathological pattern of the disease was first noted by pathologists William Chester and Jakob Erdheim in 1930.² It has recently been reclassified by the World Health Organisation as a histiocytic neoplasm and is therefore considered as a slow-growing blood cancer which may originate in the bone marrow or a precursor cell.³

A 2013 literature review showed the most common presenting symptoms as being skeletal symptoms, diabetes insipidus, neurological and constitutional symptoms.⁴ Radiologically, symmetrical osteosclerosis of the long bones has been observed. Tissue histology may show non-Langerhans xanthomatous histiocytes (i.e. containing large amounts of lipid) surrounded by fibrosis.¹ Genetically, there is evidence for mitogen-activated protein kinase (MAPK) mutations in CD34+ cells in patients with ECD. Current treatment is based on the individual. We present the case of a 64-year-old man with a diagnosis of ECD who is currently still under our care.

Case history

A 64-year-old ex-RAF pilot with a background of late-onset asthma suffered from an asthma attack and sinusitis while he was abroad. Over the next two years, he saw a number of physicians regarding his rhinitis and asthma. A further year later, he presented with a week of progressive right-sided visual loss associated with periorbital pain.

Computed tomography (CT) revealed a retro-orbital lesion, and he underwent an emergency right sphenoidotomy to decompress the optic nerve.

Two months later, he had further endoscopic sinus surgery for more tissue samples from the right maxillary antrum, right sphenoid and anterior ethmoid. He was then commenced on oral and topical steroids. Histology showed mixed acute, chronic and ulcerated mucosa with histiocytic infiltration and some multinucleated cells with scattered lymphocytes. Stains were negative for Ziehl–Neelsen, periodic acid-Schiff and Grocott's. A multidisciplinary team meeting was held, where *Klebsiella rhinoscleromatis* was suspected, but tests were only positive for pneumococcus.

Clinically, the patient seemed stable, with cessation of orbital pain, although he suffered from residual visual impairment from his previous operation. CT of the sinuses showed residual disease similar to the previous scan months previously, with no extension into the orbits, normal aeration of the mastoid cells and normal auditory apparatus.

Biopsies from both sinus operations were re-examined by immunologists, who subsequently queried a diagnosis of immunoglobulin G4 (IgG4) disease or ECD. IgG4 was deemed unlikely as both immunoglobulin and immunoglobulin G subclasses were seen to be in normal parameters and were polyclonal. The diagnosis of ECD was equivocal as although both the morphology and the immunophenotype of the histiocytic infiltrate were compatible with ECD (CD163 and CD68 positive, CD1a and S100 negative), the molecular pathology showed no mutation in *BRAF* codon 600 or within the codons of *KRAS* and *NRAS* (which has been previously documented for this disease). Further tests showed that antinuclear antibodies were negative and antineutrophil cytoplasmic antibodies

weakly positive with a 1 : 25 perinuclear pattern but negative myeloperoxidase and proteinase-3 antibodies. The weakly positive perinuclear antineutrophil cytoplasmic antibodies were deemed to be probably insignificant, as they are often associated with low-grade chronic infection. Lymphocyte subset numbers were normal.

A few months later, an isotope bone scan and CT of the sinuses, thorax, abdomen and pelvis was completed, as the bones, lung and heart are commonly affected in ECD. However, no bony involvement was seen. Whole-body positron emission tomography confirmed that there was no evidence of disease outside the paranasal sinuses.

Further surgery in the form of image-guided bilateral sphenoethmoidectomy was performed for further tissue sampling. Histology revealed possible late-stage eosinophilic angiocentric fibrosis affecting the paranasal sinuses but was initially negative for *BRAF* V600 immunostain. However, real-time polymerase chain reaction (PCR) analysis of the *BRAF* gene revealed a mutation within codon 600. In addition, the sheets of histiocytes were once again positive for CD68 PG-M1, CD68 KP-1 and negative for S-100 and CD1a, confirming the histiocytic nature of the lesion and excluding Langerhans cell histiocytosis. In light of these findings, the patient was diagnosed with Erdheim–Chester disease.

The patient was managed with oral steroids, Flixonase® Nasules®, nasal douching and radiological surveillance. He continues to be monitored by multiple specialties including respiratory, ear, nose and throat and ophthalmology.

Discussion

This patient presented unusually with ECD isolated to the sinuses, which is rare. The literature shows that nearly all patients with ECD have long-bone involvement, with radiographic findings of symmetric diaphyseal and metaphyseal osteosclerosis in the legs. Approximately 4% of patients diagnosed with ECD, however, do not have these symptoms and the diagnosis is based on histopathology and other classic organ involvement.⁵

Diagnosis of ECD histologically is made with ECD histiocytes being positive for CD68, CD163 and factor XIIIa, and negative for CD1a and Langerin (CD207). Positivity for S100 has been observed rarely. This case supports ECD as the diagnosis as the patient's histiocytes were positive for CD163 and CD68, whereas CD1a and S100 were negative. The literature indicates that there is a high frequency of *BRAF* V600 mutations in ECD as well as Langerhans cell histiocytosis.⁵ For this patient, both the first and second histology were negative but real-time PCR revealed that there was a *BRAF* V600 mutation. LCH is differentiated from ECD as Langerhans cells are positive for CD1a, S100 and Langerin. This false-negative result raises the possibility of further patients who may have been misdiagnosed due to false negative histology; thus, real-time PCR may be required for accurate diagnosis.

Figure 1 Computed tomography of the head showing bony erosion of the right superolateral wall of the sphenoid and a pneumatized anterior clinoid process.

Figure 2 a) Histiocytic infiltration. b) Histiocytes positive for CD 68 PG-M1. c) Histiocytes negative for S-100. d) Histiocytes negative for CD1a.

Interferon- α -2a currently has the largest amount of supporting evidence for the treatment of ECD; however there are no accepted guidelines for diagnosis and treatment.⁵ The patient carefully weighed up and decided against this treatment and appears to have controlled

symptoms following his surgery with the use of oral steroids and a steroid spray.

References

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