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BMJ Case Reports

Submission template for full cases

**TITLE OF CASE**

**Erdheim Chester disease – 25 year history with early CNS involvement**

**AUTHORS OF CASE** ***Please indicate corresponding author by *(after the author's name)***

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**SUMMARY** ***Up to 150 words summarising the case presentation and outcome***

We report a case of Erdheim Chester disease (ECD) with a 25-year history following initial presentation with diabetes insipidus and brainstem involvement. The exceptionally long history is particularly notable given that ECD is a life-threatening disorder and there is a recognised association between CNS involvement and poor outcome. The case is a timely reminder of the presenting features of the condition given the emergence of potential new treatment options.

**BACKGROUND** ***Why you think this case is important – why you decided to write it up***

ECD is a rare form of non-Langerhans' cell histiocytosis which was first described in 1930 by Jakob Erdheim and William Chester.[1] Currently, there are fewer than 600 documented cases in the medical literature. Given the rarity of the condition and myriad presenting symptoms, diagnosis is frequently delayed. Whilst in the past, treatment options were not available, therapeutic interventions are now recognised as being of benefit for at least some individuals, including treatment with interferon-alpha, the BRAF-V600E inhibitor, Vemurafenib, and the IL-1 receptor antagonist, Anakinra.[2,3] A natural history study is being conducted by the National Human Genome Research Institute of the National Institutes of Health and the first set of consensus guidelines regarding diagnosis and management have recently been published[3] with the aim of facilitating research and participation international clinical trials. The availability of potential treatments and options for inclusion in clinical research mean that there is an increasing need to establish the diagnosis as early as possible with the aim of avoiding morbidity and, in particular, neurological disability.

**CASE PRESENTATION** ***Presenting features, medical/social/family history***

We present the case of a lady who presented with diabetes insipidus at the age of 46 years. There was a prior history of erythema nodosum but no other past medical history. Treatment with Carbamazepine was commenced 2 years later when she developed complex partial seizures and an EEG confirmed a liability to seizures with a left temporal focus. Magnetic resonance imaging (MRI) at that time was reported to show bilateral T2 high signal change in the pons with heterogenous enhancement. The diagnosis remained uncertain despite extensive investigation including cerebrospinal fluid analysis, a gallium scintigram and Kveim test, and interval neuroimaging revealed little change. The patient was subsequently lost to neurology follow up.

Aged 55 years, a diagnosis of Coeliac disease was made on the basis of positive anti-endomysial antibodies and villous atrophy on duodenal biopsy. In her 60s, the patient developed hypertension, hypercholesterolaemia and peripheral vascular disease.

Aged 64 years, the patient re-presented to the Neurology Department with the question of whether anti-convulsant treatment could be discontinued safely given that she had been seizure-free for a protracted period. At that time, there was bilateral internuclear ophthalmoplegia and cerebellar signs. Cranial MRI demonstrated 2 enhancing mass lesions in the upper medulla and pons with involvement of the floor of the fourth ventricle, enhancement in the hypothalamus and developing hydrocephalus (figure 1). MR spectroscopy revealed raised choline and reduced N-acetyl aspartate (NAA) (figure 1). A CT of the chest, abdomen and pelvis was reported to be normal. Stereotactic pontine biopsy was undertaken. Histological analysis revealed sheets of foamy macrophages with occasional CD20-positive B cells and reactive astrocytes. Myelin loss was noted with sparse PAS-positive granules. Immunocytochemistry for JC virus was negative. Overall, the appearances were considered in keeping with inflammatory demyelination.

Clinical deterioration was rapid and persistent despite treatment with corticosteroids and plasma exchange. There was progressive hydrocephalus with development of a complex ophthalmoplegia, upbeat nystagmus, ataxia, and cognitive decline. Analysis of a further biopsy taken at the time of endoscopic third ventriculostomy was inconclusive. Repeat duodenal biopsy showed persistent villous atrophy despite adherence to a gluten-free diet.

At this time, a chest radiograph performed for investigation of aspiration pneumonia was reported to show sclerotic lesions in the proximal humeri (figure 2). (99)Technetium bone scintigraphy showed striking and symmetrical intense uptake within the distal femora and proximal tibiae, as well as in both humeri and femoral heads with a pattern pathognomonic of ECD (figure 3).

**INVESTIGATIONS** ***If relevant***

**DIFFERENTIAL DIAGNOSIS** ***If relevant***

**TREATMENT** ***If relevant***

**OUTCOME AND FOLLOW-UP**

In view of the rapid clinical deterioration with significant cognitive involvement and recurrent aspiration pneumonia, palliative treatment was instigated.

Post-mortem analysis of the brain revealed dilatation of the third and fourth ventricles with clubbing of the posterior horns of the lateral ventricles. There was a right posterior cerebral artery territory infarct which was felt to be in keeping with raised intracranial pressure. Two exophytic, spherical and lipid-filled masses occupied the fourth ventricle with extension into the cerebellum with the larger of the two measuring 35 mm x 25 mm x 20 mm (figure 4). Large swathes of foamy macrophages were seen on microscopy together with necrosis and occasional multinucleated cells. The cells were CD68-positive and S100-negative (figure 4). There was a mild degree of cerebrovascular disease throughout the cerebral white matter and the macroscopic appearance suggesting a right occipital lobe infarct was confirmed on microscopy. There was no evidence of lymphoma or carcinoma. The mucosa of the small and large bowel was normal macroscopically but was not sampled for histological analysis. BRAF mutation analysis was not undertaken.

**DISCUSSION** ***including very brief review of similar published cases (how many similar cases have been published?)***

Our patient had an exceptionally long disease history of Erdheim Chester disease with some classical features including presentation with diabetes insipidus, long bone involvement and premature cardiovascular disease. Whilst gastrointestinal involvement has been reported rarely in ECD,[4,5] this was not confirmed to be the cause of villous atrophy in this case although the lack of response to gluten-free diet is notable. No skin lesions were observed although the past history of erythema nodosum was noted.

ECD is a rare form of non-Langerhans' cell histiocytosis and lipid-laden histiocytes with eosinophilic or foamy cytoplasm infiltrate into various organs. The aetiology of the disease is not certain but it is now recognised that a very high proportion of cases have activating mutations in the mitogen activated protein kinase (MAPK) signalling pathway. It has also been suggested that the diverse clinical presentation of the disorder may reflect activation of MAPK mutations at different stages of myeloid differentiation.[6]

A very high proportion of cases are now recognised to have activating mutations in the proto-oncogene BRAF-V600E – perhaps up to 100% if a sufficiently sensitive technique is employed.[7] In the light of this, ECD is now considered a dendritic cell neoplasm with a prominent inflammatory component rather than a disorder of immune regulation.

ECD typically presents between the ages of 50 - 70 years old. A male predominance has been reported.[8] Recognised disease manifestations are myriad and include cortical sclerosis with consequent bone pain, exophthalmos, diabetes insipidus, cerebellar lesions, interstitial lung disease, pericardial thickening and retroperitoneal fibrosis, and skin lesions. Diabetes insipidus has been reported in a third of cases and is often the presenting symptom.[9] CNS involvement has been recognised to be associated with poor prognosis.[8]

Diagnosis of ECD relies on radiological and histological criteria. Radiographically, it is characterised by bilateral long bone sclerosis involving the diametaphyseal regions. Non-Langerhans' foamy histiocytes, which are positive for CD68 and negative for S100, CD207 and CD1a are seen on histological analysis.[3]

Due to the small number of cases, there have been no randomised controlled trials of therapy for ECD. The largest body of supportive evidence is for use of interferon-alpha but other treatments that have been reported include anticytokine directed therapy (anakinra, infliximab, tocilizumab), corticosteroids, cytotoxic chemotherapies, radiotherapy, and surgery (reviewed [3]). The possibility that combination therapies may be of additional value is beginning to be explored.[10] Given the uncertainties regarding optimal management, involvement in clinical studies is advised whenever possible.

**LEARNING POINTS/TAKE HOME MESSAGES** ***3 to 5 bullet points***

1. Neuroendocrine syndromes are an early feature of some infiltrative brain diseases including histiocytosis, sarcoidosis, amyloidosis, lymphoproliferative disease, Wegener's granulomatosis and infections such as tuberculosis and syphilis.
2. When an infiltrative or inflammatory pathology is being considered, explore the possibility of multi-system disease. A multidisciplinary team approach is key in reaching the diagnosis.
3. Careful radiological assessment and familiarity with the associated radiological abnormalities facilitates an accurate diagnosis of Erdheim Chester Disease

4. Referral to a specialist centre with expertise in treating Erdheim Chester Disease is recommended due to sparse clinical experience with this 'orphan' disease and the pressing need for collaborative international research.

**REFERENCES** ***Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)***


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**Figure captions**

Figure 1 Axial (A) and coronal (B) gadolinium-enhanced cranial MRI demonstrating enhancing mass lesions in the upper medulla and pons with involvement of the floor of the fourth ventricle. MR spectroscopy (C) shows markedly raised choline and reduced NAA levels.

Figure 2 Chest radiograph demonstrating sclerosis in the proximal humeri (arrows) and with evidence of old rib fracture.

Figure 3 Whole body (99)technetium bone scintigraphy revealed very striking and intense, symmetrical uptake in the distal femora and proximal tibiae, as well as in the shafts of the humeri and both the humeral and femoral heads.

Figure 4 Macroscopy autopsy specimen showing the mass which fills the fourth ventricle and which was contiguous with a second similar cerebellopontine mass. The masses were comprised of large swathes of foamy macrophages, together with necrosis and occasional multinucleated cells (B) and which were CD68-positive (C).

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