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Chinese Erdheim-Chester disease: clinical-pathology-PET/CT updates

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Summary

Erdheim-Chester disease (ECD), one type of systemic non-Langerhans cell histiocytosis, has been rarely seen and is characterized by the accumulation of foamy CD68+CD1a- histiocytes. We reported a case of ECD and reviewed the clinical features of 13 cases of ECD reported so far in China. A 53-year-old male was diagnosed with central diabetes insipidus in March 2014, followed by fever, splenomegaly and anemia in July 2014. His initial pituitary magnetic resonance imaging (MRI) revealed the absence of high signal at T1-weighted image in posterior pituitary without any lesion. A further positron emission tomography/computer tomography (PET/CT) images showed elevated metabolic activity of ^{18}F-2-fluro-D-deoxy-glucose (FDG) and low ^{13}N-NH3 uptake in the posterior pituitary, and multi-organ involvement. Biopsy at right femur lesion revealed that granulomatous infiltration of foamy histiocytes and Touton giant cells surrounded by fibrosis tissues. Immunohistochemistry stain was positive for CD68, negative for CD207/Langerin and S-100. The diagnosis of ECD was confirmed and the treatment with pegylated interferon was effective. ECD was a possible immune-related disorder concluding from the IgG4 immunohistochemistry results. We summarized the pathological manifestations for ECD and its differential diagnosis from Langerhans cell histiocytosis (LCH) and Rosai-Dorfman disease (RDD). ECD should be considered by both pathologists and clinicians in the differential diagnosis when central diabetes insipidus is accompanied with multi-organ involvement, especially skeletal system involvement, or recurrent fever.

Learning points:

- ECD should be considered when central diabetes insipidus is accompanied with multisystem involvement, especially symmetric/asymmetric bone lesions, or recurrent fever.
- PET/CT scanning was helpful for locating pituitary lesion, discovering multiple system involvement and indicating the biopsy sites.
- Conducting proper immunohistochemistry stains was important for diagnosing ECD. ECD might be correlated with immune disorder.

Background

Erdheim-Chester disease (ECD), one kind of systemic non-Langerhans cell histiocytosis, was initially denominated by Jaffe in 1972 (1). It has been very rarely reported, with only about 500 cases worldwide and only 13 cases reported

in China so far. ECD is a progressive disease with a 5-year survival rate of 68% and its etiology is still unknown. Its diagnosis relies on pathological founding. It can be easily misdiagnosed if the pathologist ignores the clinical manifestations and fails to conduct proper immunohistochemical stains. Awareness for the pathologist and the clinician may be the key factor to recognize the disease. Here, we report a case of ECD in China, focusing on clinical manifestations, pathology differentiation and the application of brain or whole body PET/CT.

Case presentation

The patient, a 53-year-old Chinese male, was diagnosed with central diabetes insipidus in March 2014. He experienced polydipsia and polyuria (increased urination to 4～6 l/day). The treatment with 0.1 mg Desmopressin per 8 h was effective to alleviate polydipsia and polyuria. In July 2014, fever appeared recurrently with chills and sweating. There were no pain symptoms.

Investigation

His hemoglobin was 8.7 g/dl (normal range (the same below): 12～16 g/dl) and immune globulin in serum was low: IgA 1.00 g/l (1.45～3.45 g/l), IgM 0.36 g/l (0.92～2.04 g/l), IgG 7.06 g/l (10.13～15.13 g/l), IgG4 0.471 g/l (<2.000 g/l). The water deprivation test revealed that the peak urine osmolality was 275 mOsm/KG post fluid restriction and 503 mOsm/KG after Desmopressin 5 IU injection. An initial MRI scan of the pituitary showed that the high signal at T1-weighted image in posterior pituitary was absent. No obvious lesion was seen around the sella turcica area or pituitary stalk. The ultrasound revealed that the spleen was large with the length of 16.7 cm and the thickness of 6.7 cm. There was no evidence for the inflectional, rheumatological or tumor associated fever. In order to find out the reason of central diabetes insipidus and fever, he underwent the whole body and brain PET/CT using FDG and ^{13}N-NH3. PET/CT scan revealed elevated metabolic activity of FDG in posterior pituitary, long bones of limbs, axial skeleton, spleen, maxillary sinus and T12 vertebrae. Isotopic tracer of ^{13}N-NH3 showed low uptake in the posterior pituitary (Fig. 1). Biopsy performed at the right femur lesion revealed granulomatous infiltration by foamy histiocytes and Touton giant cells surrounded by fibrosis (Fig. 2A, B, and C). Further immunohistochemistry stains exhibited positive for CD68, negative for CD207/Langerin and S-100. The IgG4 and IgG immunohistochemistry stains showed that a few cells with positive IgG4 or IgG, but IgG4 to IgG ratio was lower than 40% (Fig. 2D, E, and F). Integrating with the clinical manifestations, like multisystem involvement especially multifocal symmetry bone involvement, PET/CT findings and histopathology and immunohistochemical features, a diagnosis of ECD was confirmed.

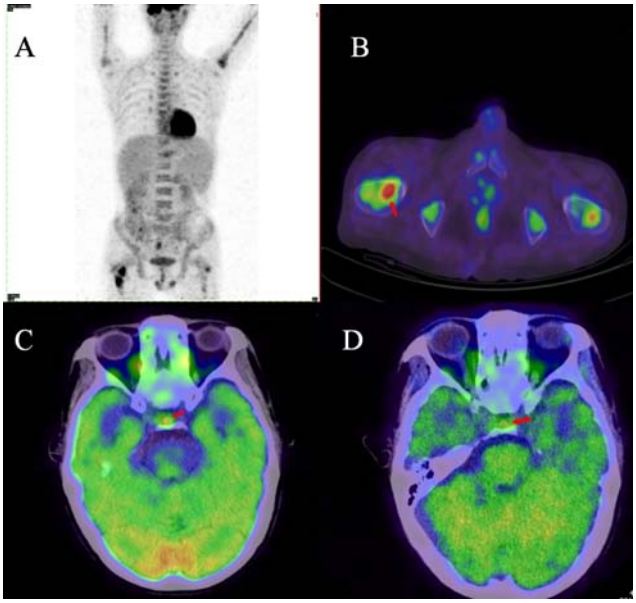

Figure 1
The PET/CT imaging characteristics of ECD in this case. (A) Coronal FDG-PET/CT images showing diffuse elevated metabolic activity in the long bones of limbs. (B) Axial ^{18}FDG-PET/CT fusion images in lower limbs showing osteolytic lesion in the right femur (arrow) and the standard uptake value max (SUVmax) was 5.8. (C) Axial ^{18}FDG-PET/CT fusion images in pituitary gland showing elevated metabolic activity in posterior pituitary (arrow) and the SUVmax was 5.6. (D) Axial ^{13}N-NH_3-PET/CT fusion images in pituitary gland showing descending metabolic activity in posterior pituitary (arrow).

Treatment and outcome

Pegylated interferon of 180 μg/week had been used subcutaneously since August 2014. Two weeks after the treatment with pegylated interferon, his fever disappeared, polyuria alleviated at reduced dose of Desmopressin, and splenomegly showed a small reduction (16.6× 6.2 cm) under ultrasound examination. He is still being followed.

Discussion

The pathogenesis of ECD is still unclear. Cruz *et al.* (2) presumed that ECD might be an autoimmune disease because ECD could be secondary to familial

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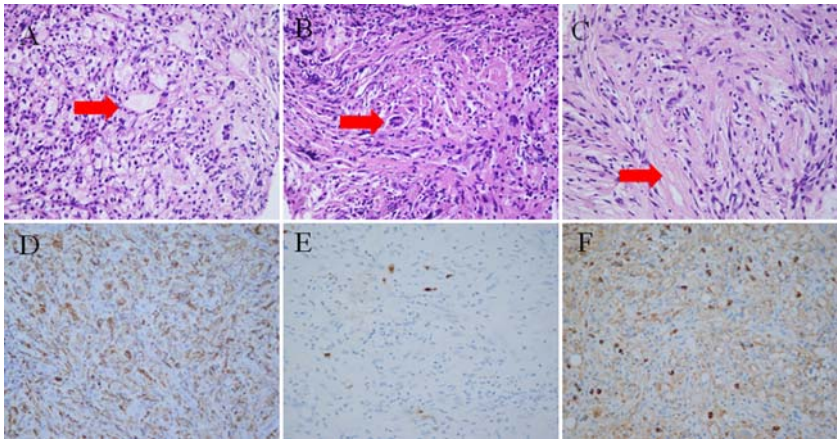

Figure 2
The histopathology and immunohistochemistry stain characteristics of ECD in this case: the lesion of right femur was composed of lipid-laden histiocytes (A) and Touton giant cells (B) nested among fibrosis tissues (C) in Hematoxylin-eosin-stained. Immunohistochemistry stain for CD68 was positive (D). IgG4 (E) and IgG (F) were positive in histiocytes (magnification, 100×).

thrombocytopenia and Hashimoto's thyroiditis. The case we reported here did not meet the diagnostic criteria of IgG4 related diseases because IgG4 to IgG ratio was lower than 40% and serum IgG4 level was within normal range. But we believe that ECD might be an immune-related disease because he had reduced serum immunoglobulin levels and some positive IgG4/IgG stains. It was reported that more than half of ECD patients had BRAFV600E mutation (3, 4). We planned to do genetic sequencing investigation later on.

Clinically, ECD is characterized by multiple organ involvement. Skeletal system is the most commonly involved, usually presenting as bone pain. Central diabetes insipidus is one of the symptoms for CNS involvement. Proptosis, periorbital infiltration and even blindness develop when eyes are affected. ECD might involve other organs and systems like kidney, adrenal, pancreas, lung, cardiovascular, retroperitoneal, skin and so on. To describe the clinical features of ECD in China, we summarized 13 case of Chinese ECD, which were published in the Chinese Journal. Overall 69.2% of them (9/13) were female and the mean age of diagnosis was 44 years old. The percentage of skeletal system, CNS, eyes, cardiovascular, skin, lung and adrenal involvement was 84.6% (11/13), 46.2% (6/13), 30.8% (4/13), 23.1% (3/13), 15.4% (2/13), 15.4% (2/13) and 7.7% (1/13) respectively.

Table 1 The key points for differentiating among ECD, LCH and RDD.

	ECD	LCH	RDD
Pathological			
Light microscopy	Foamy histiocytes or Touton giant cells nested among fibrosis	Abundant cytoplasm, coffee beans nuclear	Intracytoplasmic lymphocytes (emperipolesis)
Electron microscopy	Birbeck granules (−)	Birbeck granules (+)	Birbeck granules (−)
Immunohistochemistry			
CD207/Langerin	−	+	−
S-100	−	+	+
CD1a	−	+	−
CD68	+	+	+
Clinical manifestation	Most commonly involved in skeletal	Most commonly involved in skeletal	Most commonly involved in lymphonodus
X-ray finding	Bilateral symmetry of long bone osteoepiphysis and cortical sclerosis	Axial skeleton osseous changes	Non-specific
Therapy (primary)	IFN-α	Chemotherapy	Surgery

ECD, Erdheim-Chester disease; LCH, Langerhans cell histiocytosis; RDD, Rosai-Dorfman disease.

PET/CT, used as functional examination for pituitary diseases, is new and few reported for ECD. Seok *et al*. (5) believed that PET/CT had advantages to differentiate pituitary adenomas from cystic lesions. Zhang *et al*. (6) found that the first-pass uptake rate of dynamic ^{13}N-NH3 and standard uptake value max (SUVmax) of pituitary gland was significantly lower in hypopituitarism than healthy volunteers. The lesion in posterior pituitary was recognized through brain PET/CT scan, but not MRI. PET/CT is another approach to locate the pituitary lesion and an excellent tool in finding multiple involvements.

The diagnosis of ECD relies mainly on experienced pathologists with proper immunohistochemistry stains, especially when symmetrical skeleton system lesions are present with multiple system involvement. The pathological characteristics of ECD usually present as granulomatous disease. According to the histiocytosis classification, ECD is one kind of non-Langerhans cell histiocytosis, and it should be differentiated from Langerhans cell histiocytosis (LCH) or sinus histiocytosis with massive lymphadenopathy (SHML), also known as Rosai-Dorfman disease (RDD). The key points for differentiating among these diseases were summarized in Table 1 (7, 8).

There is no definitive successful treatment for ECD. IFN-α is the first-line treatment for those without CNS involvement. When CNS is involved, a high-dose of Methotrexate would be an option due to its rapid onset of action and excellent CNS penetration (9). For those with BRAFV600E mutation, Vemurafenib, a specific inhibitor of mutant BRAF, might be a better selection, as it suppresses proliferation of cells expressing mutated BRAFV600E proteins (10).

ECD might be an immune related disease. Pathology features was essential to distinguish ECD from LCH and RDD. Brain PET/CT scanning was an additional approach for locating pituitary lesion, and whole body PET/CT scanning helped to know multiple system involvement. ECD should be considered when central diabetes insipidus accompanied with recurrent fever, bone pain or multiple system involvement.

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Patient consent
Written informed consent was obtained from the patient for publication of this case report.

Author contribution statement
All co-authors listed contributed substantially to the preparation of this manuscript.

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