Case Report

Cytomorphology of Erdheim–Chester disease presenting as a retroperitoneal soft tissue lesion

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Published: 27 December 2011
Accepted: 30 November 2011

Abstract

Erdheim–Chester disease (ECD) is a rare, multisystem disorder of macrophages. Patients manifest with histiocytic infiltrates that lead to xanthogranulomatous lesions in multiple organ systems. The cytologic features of this disorder are not well characterized. As a result, the cytologic diagnosis of ECD can be very challenging. The aim of this report is to describe the cytomorphology of ECD in a patient presenting with a retroperitoneal soft tissue lesion. A 54-year-old woman with proptosis and diabetes insipidus was found on imaging studies to have multiple intracranial lesions, sclerosis of both femurs and a retroperitoneal soft tissue mass. Fine needle aspiration (FNA) and a concomitant core biopsy of this abnormal retroperitoneal soft tissue revealed foamy, epithelioid and multinucleated histiocytes associated with fibrosis. The histiocytes were immunoreactive for CD68, CD163, Factor XIIIa and fascin, and negative for S100, confirming the diagnosis of ECD. ECD requires a morphologic diagnosis that fits with the appropriate clinical context. This case describes the cytomorphologic features of ECD and highlights the role of cytology in helping reach a diagnosis of this rare disorder.

Key words: Cytology, Erdheim–Chester disease, fine needle aspiration, histiocytosis, langerhans cell histiocytosis, retroperitoneum, xanthomatous

INTRODUCTION

The histiocytic syndromes are a rare, heterogeneous group of neoplastic and non-neoplastic disorders that are challenging to diagnose.[1,2] They arise from a common CD34 positive progenitor cell within the bone marrow and demonstrate a pathologic accumulation of histiocytes.[1,3] They include dendritic cell related disorders such as Langerhans cell histiocytosis (LCH) and macrophage related disorders, also known as the non-Langerhans cell histiocytes (non-LCH), which include the hemophagocytic syndromes, sinus histiocytosis with massive lymphadenopathy (SHML or Rosai–Dorfman disease) and Erdheim–Chester disease (ECD). Clinically, the non-LCH are benign proliferative disorders that

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DOI:
10.4103/1742-6413.91242
can be divided into three major groups: those with i) primarily cutaneous involvement; ii) cutaneous and systemic involvement; and iii) primarily extracutaneous involvement, such as ECD.\[4^\]

ECD, also known as polyostotic sclerosing histiocytosis, is a non-LCH disorder that may be confused with LCH.\[4-7^\] Histiocytic infiltration in patients afflicted with ECD leads to xanthogranulomatous lesions that may involve multiple organ systems. Clinically, ECD demonstrates symmetrical osteosclerosis of the diaphyseal and metaphyseal regions of long bones. More than 50% of cases also demonstrate extraskeletal organ involvement, most commonly affecting the kidney, retroperitoneum, skin, brain, cardiovascular system and lung [Table 1].\[4-9^\] Less commonly, the retro-orbital tissue and pituitary gland may be involved causing exophthalmos, diabetes insipidus and shortness of breath related to cardiac tamponade. Magnetic resonance image (MRI) of her brain revealed retro-orbital and intracranial lesions involving the posterior falx and tentorium. A trans-sphenoidal biopsy was non-diagnostic due to scant cellularity. Lower limb X-rays identified areas of sclerosis in her femoral bones. The patient developed cardiopulmonary arrest and bilateral blindness. A subsequent contrast-enhanced computed tomography (CT) scan of the chest, abdomen and pelvis demonstrated a large pericardial effusion and thickening of the visceral pericardium as well as an infiltrating process in the retroperitoneum, predominately involving the perinephric spaces, left paraaortic, and interaortacaval spaces. There was also infiltration of the adrenal glands and peri-adrenal fat and extensive perivascular infiltration with encasement of the celiac artery, superior mesenteric artery, renal arteries and veins [Figure 1]. She underwent an ultrasound-guided 25-gauge fine needle aspiration (FNA) and concomitant 18-gauge core needle biopsy of the perirenal lesion. The patient was treated with corticosteroids and received whole-brain radiation. She was discharged to a rehabilitation facility and lost to follow-up after 1 year.

There are two types of histiocytes: dendritic cells and those derived from the macrophage/monocyte cell line. The dendritic cells include Langerhans cells of the skin and bronchial epithelium, as well as interdigitating and dendritic reticulum cells in lymph nodes and the spleen. They are involved in antigen presentation to lymphocytes and a subset is immunoreactive for S100 and CD1a. The monocyte/macrophage cell line consists of phagocytic cells that include tissue macrophages, osteoclasts, microglia, Kupffer cells and circulating monocytes. A subset of these cells is immunoreactive for CD68 and Factor XIIIa. The diagnosis of ECD is confirmed by tissue biopsy in the appropriate clinical setting showing histiocytes with non-Langerhans cell features. Histiocytes in ECD are immunoreactive for macrophage (CD68, CD14, CD163) and xanthogranuloma (Factor XIIIa, fascin) markers, but not for LCH (S100, CD1a) markers.\[12^\] Also, ECD histiocytes do not contain Birbeck granules ultrastructurally.

Unlike LCH in which the cytologic features are well described in the literature,\[13-17^\] the authors are aware of only one case describing the cytologic features of ECD in the literature.\[18^\] Therefore, the aim of this report is to share the unique cytomorphologic findings in another case of ECD and to highlight the key cytologic features that were helpful in reaching this challenging diagnosis.

**CASE REPORT**

**Clinical features**

A 54-year-old woman with a past medical history of type II diabetes mellitus and alleged Paget’s disease of the bone presented with progressive proptosis, exophthalmus, central diabetes insipidus and shortness of breath related to cardiac tamponade. Magnetic resonance image (MRI) of her brain revealed retro-orbital and intracranial lesions involving the posterior falx and tentorium. A trans-sphenoidal biopsy was non-diagnostic due to scant cellularity. Lower limb X-rays identified areas of sclerosis in her femoral bones. The patient developed cardiopulmonary arrest and bilateral blindness. A subsequent contrast-enhanced computed tomography (CT) scan of the chest, abdomen and pelvis demonstrated a large pericardial effusion and thickening of the visceral pericardium as well as an infiltrating process in the retroperitoneum, predominately involving the perinephric spaces, left paraaortic, and interaortacaval spaces. There was also infiltration of the adrenal glands and peri-adrenal fat and extensive perivascular infiltration with encasement of the celiac artery, superior mesenteric artery, renal arteries and veins [Figure 1]. She underwent an ultrasound-guided 25-gauge fine needle aspiration (FNA) and concomitant 18-gauge core needle biopsy of the perirenal lesion. The patient was treated with corticosteroids and received whole-brain radiation. She was discharged to a rehabilitation facility and lost to follow-up after 1 year.

**Cytological findings**

Direct smears stained with Diff-Quik (air dried) and Papanicolaou stains (alcohol fixed) and ThinPrep (CytoLyte fixed) slides were prepared from aspirated material, along with touch preparations of the core biopsies. Material collected for cell block was fixed in formalin and sections were stained with hematoxylin and eosin (HandE). The cytology samples were of low cellularity and demonstrated bland epithelioid histiocytes arranged

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\text{Table 1: Clinical features of Erdheim–Chester disease}
\]

| Patient age | Range 7–84 years (mean 53 years) |
|-------------|----------------------------------|
| Patient gender | Affects males and females equally |
| Disease location | Systemic and symmetric manifestations |
| Cutaneous manifestations | Xanthelasma and xanthomas of the face, eyelids, axillae, neck and trunk |
| Extracutaneous manifestations | Weakness, fever, long bone sclerosis, proptosis, fibrosis of lung, kidney and retroperitoneum, CNS involvement including diabetes insipidus, ataxia, and behavioral disorders |
| Clinical outcome | Progressive disease with high fatality rate, mainly due to lung fibrosis causing respiratory/cardiac failure or renal failure from retroperitoneal fibrosis |
in clusters as well as individual foamy macrophages and occasional binucleated and multinucleated histiocytes [Figure 2]. The nuclei of these histiocytes did not have grooves or pseudoinclusions. Mitoses were not observed. The FNA also contained scant fibrous tissue fragments that contained focal admixed small lymphocytes. Eosinophils were absent. There was insufficient cell block material to perform ancillary studies.

**Histopathologic findings**

The core biopsy showed predominantly dense fibrotic tissue associated with bland spindled cells and epithelioid histiocytes that were focally aggregated in loose clusters [Figure 3]. No features of malignancy (atypia, necrosis, mitoses) were seen. A Masson trichrome stain highlighted the presence of dense collagen fibrosis.

**Immunohistochemical findings**

Immunohistochemical stains performed on the core biopsy [Figure 4] showed that the spindled cells were positive for CD34 and that both spindled and epithelioid cells were positive for CD163, Factor XIIIa and fascin, but were negative for pankeratin, S100, beta-catenin, CD117, desmin, actin and calponin. CD68 stained the focal clusters of epithelioid histiocytes. CD45 (LCA) and bcl-2 highlighted the scattered lymphocytes. Ki67 staining was not increased in lesional cells.

**DISCUSSION**

The diagnosis of ECD in our patient, initially established on clinical and radiological grounds, was confirmed by appropriate morphologic evaluation. ECD is a rare, non-inherited disease of uncertain pathogenesis first described in 1930 by Chester as a distinct form of "lipogranulomatosis with bony alterations."[19] It is now known to be a primary disorder of monocytes–macrophages that exhibit distinct...
The diagnosis of ECD typically requires a biopsy of involved tissues, since this disease must be distinguished from the more common LCH, with which it shares similar clinical features. The histopathology of ECD is well characterized and usually shows infiltrates of monomorphic foamy (xanthomatous) macrophages, scattered multinucleate (Touton) giant cells and interspersed chronic inflammatory cells (predominantly lymphocytes) surrounded by fibrosis. While eosinophils may rarely be seen in ECD, they tend to be fewer in number than the eosinophilia observed in specimens procured from patients with LCH. ECD must be distinguished from other histiocytic conditions (e.g. LCH, hemophagocytic lymphohistiocytosis), dendritic cell disorders, granular cell tumor, metastatic solid and hematopoietic neoplasms (e.g. renal cell carcinoma, oncocytic neoplasms) and reactive conditions (e.g. granulomas, malakoplakia). It is important not to dismiss such a case of ECD as merely benign fibrous tissue with associated histiocytes. Thus, clinical and radiological correlation along with appropriate immunostaining in clinically suspicious cases can be very helpful given the bland, benign-appearing nature of these lesions. A comparison of the pathology between ECD and LCH is shown in Table 2. The foamy macrophages of ECD demonstrate non-Langerhans features including lack of nuclear grooves, absence of Birbeck granules and immunoreactivity for CD68 (PGM1), lysozyme, α-1-antitrypsin, CD163, Factor XIIIa, CD14 and fascin, with concomitant negative staining for CD1a and Langerin. There are some reported cases of ECD in which histiocytes demonstrated S100 positivity.\(^{[11,29]}\) Cytologic atypia (e.g. prominent nuclei and spindle cell sarcoma-like areas), as may be identified in histiocytic sarcoma and dendritic cell sarcoma, is not a feature of ECD. No consistent cyogenetic or molecular genetic abnormalities have been identified with ECD.

The cytopathology of ECD is not yet characterized. To the best of our knowledge, we are aware of only one other case report describing the cytologic features of ECD in the literature.\(^{[18]}\) In this other case report, the diagnosis of ECD was made on an intraoperative squash preparation from a brain lesion of a 26-year-old young man. The squash preparations showed a mixed cellular proliferation of lymphohistiocytic elements along with large, multinucleated cells with vesicular nuclei, prominent nuclei and abundant cytoplasm. In our case, the specimen was of low cellularity due to the associated fibrosis; however, there were foamy histiocytes including binucleate and multinucleated cells. Obtaining a concomitant core biopsy in such cases is therefore recommended. Unlike LCH, these macrophages neither exhibited nuclear grooves, pseudo'inclusions or dendrite-like cytoplasmic processes, nor were associated with eosinophils. The cytologic findings of deep-seated juvenile xanthogranulomas may show similar features.\(^{[30,31]}\)

Albeit that ECD is a rare condition, patients presenting with the clinical features of this histiocytosis will likely require a pathologic evaluation during their work-up in order to determine the correct diagnosis. This case not only highlights the cytologic features of ECD that may be encountered, but also alerts cytologists to consider this non-Langerhans histiocytic disorder in cases showing xanthogranulomatous infiltration.

### Table 2: Comparison of the pathology in Erdheim–Chester disease and Langerhans cell histiocytosis (LCH)

| Pathology          | **ECD**                                      | **LCH**                                      |
|--------------------|----------------------------------------------|----------------------------------------------|
| Cytology           | Foamy histiocytes, Touton-type giant cells, scant lymphoplasmacytic infiltrate and rarely eosinophils. Histiocytes have no nuclear grooves, pseudoinclusions or dendrite-like cytoplasmic processes | Langerhans cells with nuclear grooves, pseudoinclusions and occasional dendrite-like cytoplasmic processes. Associated acute and chronic inflammatory cells including eosinophils with Charcot–Leyden crystals |
| Histopathology     | Sheets or clumps of infiltrating foamy macrophages, few Touton giant cells and scattered lymphocytes surrounded by fibrosis | Sheets of Langerhans cells admixed with inflammatory cells, mainly eosinophils, and scant stroma |
| Immunoprofile      | Positive: CD68, lysozyme, α-1-antitrypsin, Factor XIIIa, CD163, fascin Negative: S100, CD1a, Langerin | Positive: CD68 (dot-like paranuclear staining), S100, CD1a, Langerin Negative: Fascin (but may have variable staining) |
| Ultrastructure     | No Birbeck granules                          | Birbeck granules present                     |

ECD: Erdheim–Chester disease, LCH: Langerhans cell histiocytosis
COMPETING INTEREST STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interests.

AUTHORSHIP STATEMENT BY ALL AUTHORS

All authors of this article declare that they qualify for authorship as defined by ICMJE. All authors are responsible for the conception of this study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT BY ALL AUTHORS

As this is a case report without patient identifiers, approval from Institutional Review Board (IRB) is not required at our institution.

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