Abstract. Erdheim-Chester disease is a rare form of non-Langerhans' cell histiocytosis characterized by multi-system infiltration by xanthogranulomas composed of foamy histiocytes surrounded by fibrosis. Approximately 400 cases have been reported in the literature, and the recent increase in the number of cases is likely due to the increased awareness of its associated morbidity and mortality. The etiology of this disease remains unknown, the clinical course is variable and treatment is still not well-established. The objective of this review is to describe the pathogenesis, clinical manifestations, and diagnosis of this rare disorder, and to review its prognosis and treatment. Erdheim-Chester disease (ECD) is a rare form of non-Langerhans' cell histiocytosis, It was first described in 1930. Approximately 400 cases have been reported in the literature.

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans' cell histiocytosis characterized by multisystem infiltration by Cluster of Differentiation 68 (CD68) positive foamy histiocytes surrounded by fibrosis (1). It was first described in 1930. Fewer than 500 cases have been reported in the literature.

Etiology and Pathogenesis

The etiology and pathogenesis of ECD are poorly-understood. The clonal nature of this disease is still controversial. Although occasional clonal cytogenetic aberrations have been identified, none are pathognomonic or diagnostic of ECD. Stoppacciaro et al. demonstrated that a cytokine and chemokine network similar to that described in Langerhans' cell histiocytosis exists in ECD lesions (2). Secretion of interleukin (IL)-6 and cysteine x cysteine (CXC) chemokine ligand 8/IL-8 (CXCL8/IL8) plays a major role in recruitment and activation of histiocytes and inflammatory cells (3). This process is regulated by tumor necrosis factor, which is also expressed in ECD lesions and which activates other downstream inflammatory factors, further worsening tissue damage. In addition, chemokines expressed by ECD histiocytes are thought to attract inflammatory cells including T helper-1 (Th1)-type T-lymphocytes expressing chemokine receptors, which, in turn, drive activation and chemokine production by histiocytes (2, 4).

Clinical Presentation

Patients with ECD have a variable clinical course, ranging from asymptomatic to fatal, depending on the extent and distribution of the disease (Table I). Bone pain represents the most common symptom and usually involves the lower limbs. Typical radiological findings, including symmetric diaphyseal osteosclerosis, or symmetric uptake seen in the long bones of the extremities using bone scintigraphy, are almost pathognomonic of the disease. Bone involvement is the first manifestation of ECD in half of all patients. It also becomes symptomatic in about 50% of patients over the course of the disease (5).

The second most common involved organ is the cardiovascular system which is affected in 77% of the cases. Periarterial infiltration usually has little clinical significance except in the case of renovascular infiltration, which may cause systemic hypertension, usually corrected by renal artery stenting (6). Pericardial infiltration causing tamponade, predominantly right sided myocardial infiltration, valvular involvement occasionally requiring valve replacement and peri-coronary artery infiltration that may cause potentially fatal myocardial infarction have been reported (6-12).
Brain involvement occurs in 51% of the cases and is thought to be the only major predictor of worse prognosis in patients with ECD (13). In a comprehensive neurological series of patients with ECD, Lachenal et al. reported that cerebellar (41%) and pyramidal (45%) manifestations were the most frequent (14). Other neurological symptoms include seizures, headache, psychiatric manifestations and paroxysmal dystonia. Recently published case reports mention that ECD might present as an intramedullary spinal cord lesion (14-18).

Pulmonary involvement is also common. Arnaud et al. reported that 53% of patients have some degree of lung parenchymal infiltration and 41% have pleural infiltration (19). In another cohort of 53 patients, Arnaud et al. showed similar results, with 43% of their cases having lung infiltration (13). However, both studies concluded that pulmonary involvement was not a predictor of worse prognosis for ECD, contrary to what has been reported in earlier studies.

Orbital involvement, which is often bilateral and manifests as exophthalmos due to retro-orbital infiltration, is found in 27% of ECD patients (20). Occasionally it may be resistant to treatment, requiring surgical debulking (21, 22). Xanthelasmas of the eyelids or the periorbital spaces were also reported in 18% of the patients (20).

Diabetes insipidus is a characteristic endocrine manifestation of ECD. It is secondary to hypothalamic or pituitary infiltration, which may lead to other endocrinal abnormalities such as hyperprolactinemia or gonadotropin insufficiency (20, 23). Haroche et al. reported in 2007 seven cases of ECD with involvement of the adrenals. Diagnosis was established radiologically except for one case which was confirmed via biopsy. However, only one case had symptomatic adrenal insufficiency (24). Renal involvement is reportedly present in about 11% of ECD cases. Renal disease consists of obstructive uropathy due to retroperitoneal fibrosis or renal histiocytic infiltration. Symptoms commonly include abdominal pain, dysuria and possible development of hydronephrosis and renal insufficiency that may require hemodialysis (25-27). Retroperitoneal involvement leading to peri-renal or ureteral obstruction and causing renal impairment has been reported in 29-59% of patients with ECD (20, 28, 29).

**Diagnosis**

The diagnosis of ECD is often challenging because of the rarity of the disease and its multi-organ involvement. Tissue biopsy, preferably of an osteosclerotic bone lesion if possible, is crucial for diagnosis. Histopathological examination usually shows foamy S-100-negative and cluster of differentiation 68 (CD68)-positive histiocytes as the principal cells, surrounded by fibrosis and inflammatory cells, such as lymphocytes, plasma cells, and Touton-type giant cells (30). CD68-positive and CD1a-negative immunohistological staining helps to differentiate it from Langerhans' histiocytosis (20, 24) (Table II). A combination of clinical assessment, pathological examination and immunohistochemical staining is used to differentiate ECD from the other rare types of non-Langerhans’ histiocytosis as shown in Table III (31).

Laboratory workup includes complete blood count, chemistries, and urine electrolytes if diabetes insipidus is suspected. Imaging studies include magnetic resonance imaging (MRI) of the brain, a computed tomographic (CT) scan or an MRI of the entire aorta, a cardiac MRI, a CT scan of the chest, abdomen, and pelvis, and a transthoracic echocardiography. An MRI of the spinal cord is only necessary if the patient has signs or symptoms of spinal cord involvement.

No clear staging, prognostic, or scoring system for ECD has been established. It is suggested that 18F-fluorodeoxyglucose positron-emission tomography (PET scan) and C-reactive protein elevation may predict disease activity (32, 33). A retrospective study of 31 patients with ECD showed a variable sensitivity of PET scanning among the different organs studied. However, in one study, its specificity remained helpful in the assessment of CNS involvement, as well as in the earlier detection of treatment response as compared to brain MRI, and in the assessment of the cardiovascular system (32).

<table>
<thead>
<tr>
<th>Organ involved</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Skeletal</td>
<td>96%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>77%</td>
</tr>
<tr>
<td>CNS</td>
<td>51%</td>
</tr>
<tr>
<td>Orbital</td>
<td>27%</td>
</tr>
<tr>
<td>Urologic</td>
<td>11%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>43-53%</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Rare</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>29-59%</td>
</tr>
</tbody>
</table>

**Table II. Differential diagnosis of Erdheim-Chester disease (ECD) and Langerhans’ cell histiocytosis (LCH).**

<table>
<thead>
<tr>
<th>Marker</th>
<th>ECD</th>
<th>LCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-100 protein</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Group 1 CD1a glycoproteins</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>CD68</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Birbeck granules</td>
<td>–</td>
<td>+</td>
</tr>
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</table>

**Table I. Organ involvement in Erdheim-Chester disease (ECD)**
Treatment

Various therapies for ECD have been reported. Interferon-alpha was shown to improve survival and is currently the standard first-line treatment for patients with ECD (34). Its mechanism of action remains unclear. The dose used is 3-9 MIU three times a week. Pegylated interferon-alpha (135-200 μg once a week) has also been used. Higher doses are indicated for progressive disease unresponsive to lower doses, and in cases of CNS or cardiovascular involvement (13). However, interferon therapy can be associated with severe side-effects including severe asthenia, myalgia, pruritis and thrombopenia, which may require cessation of therapy (35). Other treatment options include recombinant human interleukin-1 receptor antagonist, cladribine, tyrosine kinase inhibitors, and autologous hematopoietic stem cell transplantation (20, 28, 36-39). Corticosteroids, vinblastine, vincristine, cyclophosphamide, doxorubicin, cyclosporine and radiotherapy have also been used (20, 29, 40).

V-raf murine sarcoma viral oncogene homolog B1 \((BR\text{F})\) \(V600E\) gain-of-function mutations have been reported in 54% of cases of ECD. Vemurafenib, an inhibitor of mutant \(BR\text{F}\) that has shown some efficacy against melanoma and hairy-cell leukemia associated with the \(BR\text{F}\) \(V600E\) mutation, was used in the treatment of three patients with refractory ECD carrying the \(BR\text{F}\) \(V600E\) mutation. The patients in the study improved clinically within a few days, with normalization of C-reactive protein value and substantial regression of lesions on PET scan. MRI studies showed that perivascular sheathing regressed, and heart infiltration improved markedly one to two months after treatment. However, all patients developed a rash, requiring dose reduction of vemurafenib (41, 42). Furthermore, among patients with ECD treated with vemurafenib, one patient showed persistent bone uptake on follow-up PET assessment at four months, despite normalization of C-reactive protein level and lack of clinical symptoms (41). This study provides an exciting mean of targeted approach in treating ECD, which should be studied further as a single agent or in combination with other treatment modalities.

Prognosis

Prognosis of patients with ECD is variable and depends on its extent and distribution. A 2011 multi-center observational cohort of 58 patients showed 1-year and 5-year survival rates of 96% and 68%, respectively. CNS involvement and treatment with interferon-α and/or Pegylated interferon-α were found to be major predictors of survival in these patients. Other causes of mortality included pulmonary infection, myocardial infarction, gastrointestinal hemorrhage, metabolic abnormalities and multisystem organ failure due to various causes (13).

Future Directions

With the significant progress in identifying molecular aberrations and mutational abnormalities in a variety of disorders, efforts should be dedicated to establishing molecular defects in ECD. The documented presence of \(BR\text{F}\) mutation in 54% of patients with ECD suggests a common pathological pathway with other disorders such as melanoma and hairy cell leukemia. Drugs that have been shown to be effective in melanoma such as vemurafenib, IL2, and ipilimumab, as well as drugs that are curative in hairy cell leukemia, such as pentostatin, cladribine, and rituximab, need to be studied in patients with ECD.
Conflicts of Interest

The Authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References


