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A Rare Presentation of Erdheim-Chester Disease Overlaped with Langerhans Histiocytosis

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Abstract

Erdheim-Chester Disease (ECD) is a rare condition and has various differential diagnoses with other forms of histiocytosis, classified as one of non-Langerhans histiocytosis. The diagnosis of this condition remains challenging because its presentation includes non-specific systemic manifestations that can affect different organs caused by deposition of lipids and fibrosis. Most common include bone pain followed by progressive weakness and different lung manifestations. This case is about a rare presentation of ECD with Langerhans Histiocytosis as overlap syndrome, with findings of both diseases in a middle aged woman that presented dyspnea as the first symptom. The patient was treated initially as heart failure and remained without any improvement, being admitted to investigate. After a stricted follow-up, bone and lung involvement were noticed and a skin biopsy unveiled xanthomatized macrophages accompanied by Touton giant cells. This condition remains an important clinical entity and should provide new insights for clinicians dealing with respiratory diseases.

Keywords

Erdheim-Chester, Langerhans Histicytosis, Pulmonary Histiocytosis

1. Introduction

Erdheim-Chester Disease (ECD) is a rare condition and a type of histiocytosis non-Langerhans with unknown etiology that shows systemic manifestations that affect bones, central nervous system, eyes, lungs, kidneys and retroperitoneum. Although being classified as one type of histiocytosis, ECD and Langerhans his-

tiocytosis remain as diseases with different etiology and the association between them is a rare condition with its diagnosis being made by histopathology. The diagnosis of the diseases has been increasing over the years and remains a challenge for the clinician. Histiocytes are cells derived from myeloid precursors (which can develop into dendritic cells, monocytes and macrophages) and their disorders named histiocytoses have been previously divided based on immunohistochemical profile and presumable origin of their cells. The histiocytosis was classified in 1987 by the Working Group of the Histiocyte Society in langerhans cells, non-langerhans and malignant histiocytosis. Erdheim-Chester disease (ECD) is a rare form of non-Langerhans-cell histiocytosis, associated in more than 50% of cases of mutation from BRAF (V600E). The inflammation and fibrosis seem to be the most important factors associated with the pathogenesis and organ dysfunction in ECD, resulting from a complex network of cytokines and chemokine-regulated responsible for histiocyte recruitment and accumulation in the tissue lesions. Langerhans histiocytosis is a disease that has characteristics of both an abnormal reactive process and a neoplastic process and can involve multiple organs, mainly bone marrow, lungs, liver, skin, lymph nodes. The presentation and organ involvement interfere directly with the prognosis.

This report is about a patient that presented an overlap syndrome of both diseases.

2. Case Report

A 51-year-old woman, farmer, mixed race, born in and living in Fortaleza, CE, Brazil, non-smoking, started experiencing an isolated case of progressive adynamia four years ago, which hindered her daily life activities. Approximately 3 months after admission, she developed dyspnea associated with moderate exertion, which progressed to light exertion, accompanied by edema of the lower limbs. She sought hospital care and the case was then treated as heart failure (HF) syndrome and referred for outpatient follow-up. One month after admission, she began to experience ventilatory-dependent chest pain, which is why she sought medical assistance again. Given the clinical history and chest radiography, it was considered a pulmonary infectious exacerbation, and antibiotic therapy with levofloxacin was initiated. She was instructed to investigate tuberculosis with sputum smear microscopy in the Primary Care. She presented new clinical decompensation despite the treatment, developing recurrent afternoon fever. She was then admitted to hospital to optimize the HF treatment and referred for investigation at the Pulmonology Service. Upon admission physical examination, the patient presented a regular general condition, hypocolored, hydrated, eupneic, alert, conscious and orientated. Her vital signs were within normal range: blood pressure at 120 × 80 mmHg, heart rate of 90 beats per minute, respiratory rate of 18 breaths per minute, and peripheral oxygen saturation of 96% while breathing room air. On cardiovascular examination, she displayed a regular heart rate and normal heart sounds devoid of murmurs. Lung auscultation revealed clear breath

sounds throughout. During abdominal examination, bowel sounds present and the abdomen was soft on palpation with the liver edge palpable at 5 cm from the right costal margin. Peripheral pulses were found to be full and symmetrical. The dermatological examination drew attention to multiple flat, hyperchromic, irregular and diffuse macular lesions on the anterior surface of the lower limbs, in addition to nodular formations on the proximal portion of both tibias (**Figure 1**).

Detailed anamnesis revealed a previous history of fractures in the right clavicle and ankle after low-intensity trauma that would have led to follow-up at a tertiary Endocrinology service due to severe osteoporosis and clinical suspicion of Paget's disease. Family history mentions that the mother had asthma and the father died of heart disease. Initial biochemical tests showed hypochromic and microcytic anemia, with an iron profile suggestive of iron deficiency anemia hemoglobin 11 g/dl (normal 11.5 to 16.4 g/dl), iron 13 µg/dl (normal 65 to 130 µg/L), ferritin 81 ng/ml (normal 10 to 160 ng/ml). Renal function was unaltered (creatinine of 0.76 mg/dl - normal 0.6 to 1.2 mg/dl - and urea 37 mg/dl - normal < 40 mg/dl). The erythrocyte sedimentation rate was elevated at 78 (normal range: 7 to 15 mm in women), and C-reactive protein (CRP) measured 8.57 mg/dl (normal range: < 0.5 mg/dl). The antinuclear factor tested positive without a specific pattern described. Serology for HIV 1 and 2, hepatitis B and C, as well as syphilis, returned negative results. Alkaline phosphatase was at the upper limit of normal at 298 U/L (normal range: 65 to 300 U/L), and calcium levels were within the normal range at 8.4 mg/dl (normal range: 8.4 to 10.6 mg/dl). Alkalin phosphatase in the upper limit of 298 U/L (normal 65 to 300 U/L) and normal calcium 8.4 mg/dl (normal 8.4 to 10.6 mg/dl).

The chest X-ray showed an interstitial pattern of pulmonary involvement, increased cardiothoracic index, mediastinal widening and consolidated fracture of the right eighth costal arch (**Figure 2**).

The transthoracic echocardiogram (TTECHO) demonstrated preserved left ventricular systolic function with an ejection fraction of 64% (evaluated using the Teicholz method). Pericardial thickening and effusion were visualized, in addition to infiltration of the lateral wall of the right atrium adjacent to the lateral leaflet of the tricuspid valve and interatrial septum, measuring 3.2 cm × 2.2 cm, suggestive of cardiac pseudotumor (**Figure 3**).

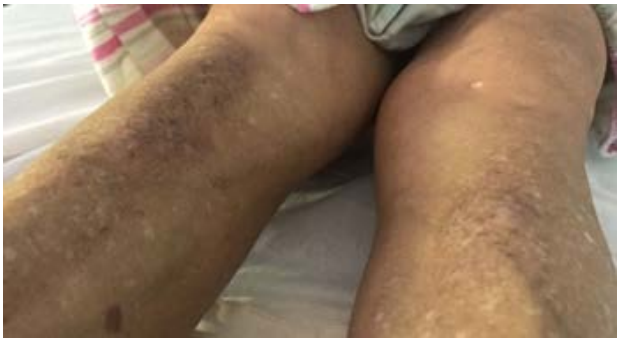

Figure 1. Xanthomatous macular lesions in the pretibial region bilaterally.

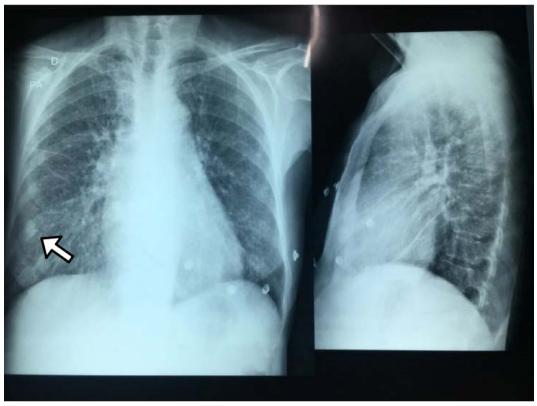

Figure 2. Chest X-ray PA and Profile: Diffuse interstitial involvement with a reticulonodular pattern, increased cardiothoracic index, mediastinal widening and consolidated fracture of the right eighth costal arch (arrow).

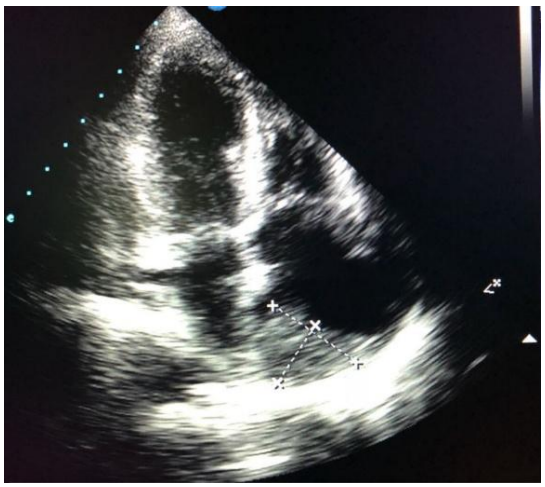

Figure 3. Transthoracic echocardiogram showing infiltration of the lateral wall of the right atrium measuring 3.2 × 2.2 cm, suggestive of cardiac pseudotumor.

High-resolution chest tomography (HRCT) showed: thickening of the interlobular septa and bronchial walls, associated with centrilobular and acinar nodules in the apical and anterior segments of the lung and diffuse areas of ground glass. There was no lymph node enlargement or pleural effusion. Contrast-enhanced chest CT revealed thickening of the entire aorta, with visualization of atrial infiltration (**Figure 4**).

Bronchoscopy showed the left bronchial tree with mucosa with a hyperemic and edematous appearance. Bronchoalveolar lavage was collected and transbronchial biopsy was performed. The lavage cytology showed moderate cellularity represented by few squamous, cylindrical, ciliated epithelial cells, neutrophils and macrophages. The AFB test and the rapid molecular test for tuberculosis in the lavage were negative. The histopathological study showed a mild lymphoplasmacytic interstitial infiltrate. The patient underwent videopleuroscopy for biopsy of the pericardium and atrial lesion, in addition to collection of fluid for cytology and culture. The histopathological study showed: chronic fibrous peri-

carditis, with nonspecific chronic inflammatory infiltrate, essentially lymphoplasmacytic with foci of fat necrosis, without signs of malignancy in the sample and the atrial lesion fragment showed young granulation tissue with fibrosis and inflammation, also without signs of malignancy in the sample. In the context of tibial radiographs that showed possible lytic and blastic lesions (Figure 5), a bone scintigraphy was requested, which showed an extensive area of osteoblastic activity in the bones of the forearms, proximal and distal portions of the humeri, distal femurs and proximal portions of the tibia left and hindfeet, in the T10, T11, L2 and L3 vertebrae, upper portion of the left acetabulum, anterior ends of some costal arches bilaterally, posterolateral portion of the approximate height of the right ninth costal arch (Figure 6). Myelogram revealed medullary hyperplasia without infiltration signs and remarkable megakaryocyte hyperplasia with intense plaquetosis.

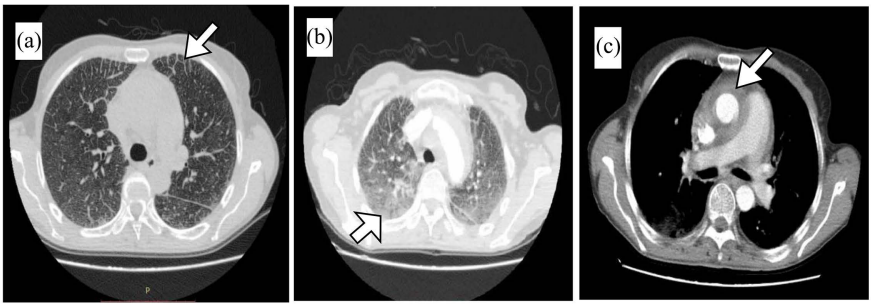

Figure 4. Chest CT showing (Arrows): (a)—Thickening of interlobular septa; (b)—Diffuse ground glass, predominantly in basal portions bilaterally; (c)—Mediastinal thickening with coating of the thoracic aorta (Coated Aorta).

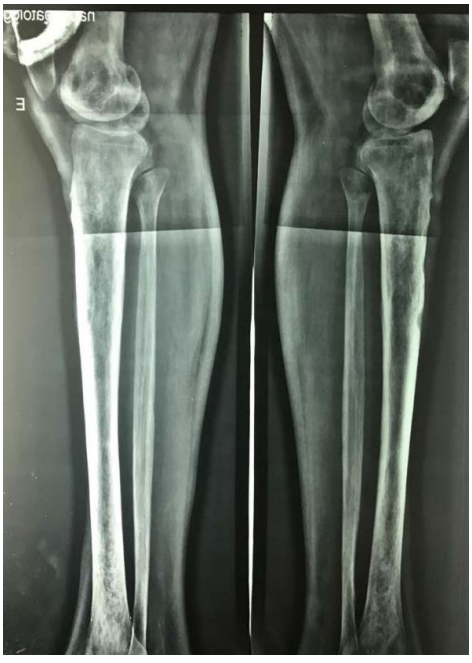

Figure 5. Tibia radiography showing reduced bone density associated with osteoblastic and osteoclastic areas of injury.

The interpretation of the examination suggested that the findings were compatible with Erdheim-Chester disease. Under clinical suspicion of ECD and due to the skin involvement in this case, a biopsy of the pre-tibial skin lesion was chosen. Histopathology showed subcutaneous tissue with proliferation of xantomized macrophages and Touton giant cells with lymphoplasmacytic infiltrate. Follow-up with immunohistochemical evaluation revealed positive markers for the presence of CD1a, S100E CD68, suggesting Langerhans histiocytosis (**Figure 7**).

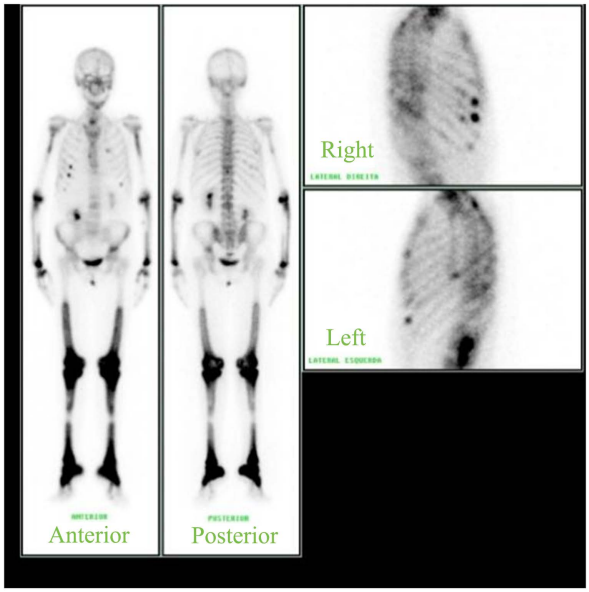

Figure 6. Bone scintigraphy with 99mTc-MDP showing extensive symmetrical lesions with a marked increase in osteoblastic activity.

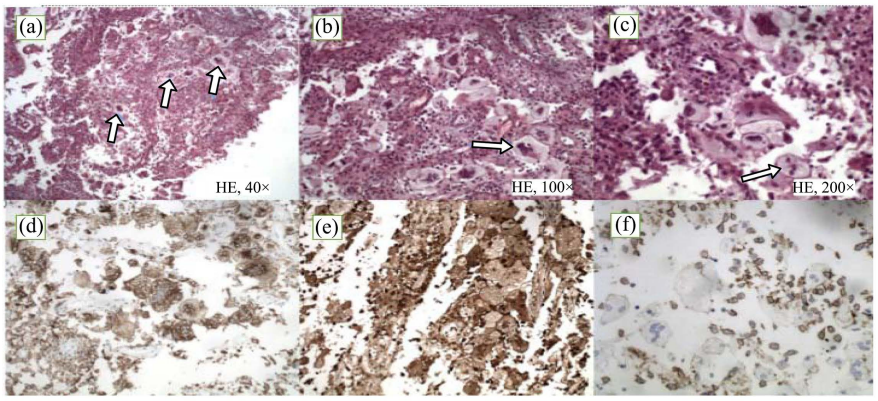

Figure 7. (a) and (b)—Different magnifications of subcutaneous tissue showing proliferation of xantomized macrophages (arrows), giant cells and polymorphous lymphoplasmacytic infiltrate. (HE); (c)—Touton-type xantomized giant cells with focal hemophagocytosis Arrow: xantomized macrophage engulfing mature lymphocytes (hemophagocytosis). (HE, 200×); (d)—Diffuse expression of macrophage marker CD68 (Immunohistochemistry); (e)—Nuclear and cytoplasmic staining of S100. (Immunohistochemistry); (f)—Expression of CD1a in 50% of xantomized cells and giant cells. (Immunohistochemistry).

The clinical findings and results of complementary exams suggestive of ECD, added to the histopathological finding of Langerhans histiocytosis, concluded that it was a case of overlap, also known in the literature as mixed histiocytosis. Oral therapy with prednisone 0.5 mg/kg/day was started. The patient was referred for joint follow-up with the hematology service for specific therapy with Interferon. Despite treatment, dyspnea persisted and the clinical condition progressively deteriorated. Eighteen months after diagnosis, there was a new hospital admission in which the patient developed bone marrow failure, neutropenia and death.

3. Discussion

We report a case of co-occurrence of ECD and HL. Patients with mixed histiocytosis present characteristics very similar to patients with isolated LH or ECD, except for the age at which the disease presents. In the literature, the average age of presentation of mixed histiocytosis is 43 years, of ECD in patients aged around 57 years and of LH in patients with a mean age of 30 years [1]. In our case report, the patient manifested symptoms at 49 years.

Patients with ECD have a variable clinical course, ranging from asymptomatic patients to fatal cases, depending on the extent and distribution of the disease. Bone pain involving the lower limbs is the most common symptom, which can be investigated through radiographic studies, with findings of symmetric diaphyseal osteosclerosis and/or scintigraphy showing symmetric uptake in long bones of the appendicular skeleton, findings considered almost pathognomonic of ECD [2]. Distribution of sclerotic lesions differ from LH. In the latter, there is more involvement of the axial skeleton and proximal portion of the limbs. The patient in question did not present bone symptoms, which can occur in 50% of cases during the course of the disease, but she had a history of non-traumatic fractures and radiological studies were consistent with ECD [3].

Cardiovascular involvement can occur in up to 77% of ECD cases, with arterial and cardiac involvement. Arterial lesions are asymptomatic, however periarterial fibrosis of the thoracic and abdominal aorta is notably present in 56% to 85% of patients with ECD [4] [5]. Fibrosis is the result of histiocytic infiltration of the adventitial layer of the vessels, causing circumferential thickening that can be visualized on contrast-enhanced tomography of the chest. Direct infiltration of arterial structures is not characteristic of Langerhans Histiocytosis [6] [7] [8].

Cardiac involvement is more noticeable in ECD and almost never occurs in LH. Although ECD can affect any segment of the heart, the most frequent findings are pericardial infiltration and pericardial effusion, which are observed in up to 42% of patients. Myocardial infiltration is detected in more than a third of the patients, with the most common finding being right atrial pseudotumor (30% - 37%) followed by infiltration of the atrioventricular groove [9] [10]. Cardiac lesions are extremely rare in LH, and if present, they should be raised suspected ECD-LH overlap [11].

Involvement of the respiratory system can occur in up to half of patients with DEC and there is no correlation with smoking, unlike pulmonary HL, in which, at diagnosis, 90% of patients are active smokers [12]. Pulmonary involvement in histiocytosis is often asymptomatic, which may rarely manifest as dyspnea and/or non-productive cough.

Radiologically, pulmonary involvement may show involvement of both the parenchyma and the pleura. Simple chest radiography helps in the differential diagnosis because in ECD it does not usually show changes, while in LH non-specific abnormalities may be present such as bilateral diffuse nodular or reticulonodular opacities. Chest HRCT in ECD may demonstrate mediastinal infiltration, pleural thickening/effusion as well as interstitial involvement with interlobular septal thickening, multifocal ground-glass opacities and centrilobular nodules [13]. In LH, the tomography initially demonstrates multiple nodules that can vary from millimeters to 2 centimeters, some with central cavitation. In more advanced disease, cysts begin to predominate. Pulmonary function tests, in both ECD and LH, may be normal or show a reduction in lung volumes as well as a reduction in the diffusion capacity of carbon monoxide. In patients with LH in the more advanced cystic form, airflow limitation and hyperinflation may occur [14].

Bronchoscopy can be used as an auxiliary resource in the differential diagnosis, especially in patients with ill-defined pulmonary involvement. In ECD, bronchoalveolar lavage fluid may contain macrophages and foamy histiocytes [15], while the occurrence of more than 5% of CD1a lymphocytes is highly related to HL. Lung tissue biopsy presents a risk of complications (for example, pneumothorax) and has low sensitivity for histopathological diagnosis, and it is therefore not recommended.

Histopathological confirmation of histiocytosis is generally performed by biopsy of non-pulmonary sites. For diagnosis, multiple biopsies may be necessary due to the sparse nature of involvement and the varying degree of fibrosis and inflammatory infiltrate in the affected organs. Although bone lesions are the first localized focus of the disease, obtaining satisfactory material for histopathological processing is hampered by the decalcification process, which can compromise the complementary immunohistochemical study [2]. In the case presented, we chose to address the skin lesions on the pre-tibial face due to the ease of obtaining material.

In ECD, tissue lesions may demonstrate typical infiltration of foamy histiocytes interspersed or not with fibrosis. Touton giant cells are often present. In immunohistochemistry, histiocytes are positive for CD68, CD163 and factor XIIIa, and negative for Cd1a and Langerin (CD207) [16]. Positivity for S100 has rarely been observed. This differentiates it from LH, in which the cells are positive for Cd1a, S100 and Langerin (**Table 1**). More recently, research into the BRAFV600E gene mutation in histopathological samples shows promise both in isolated ECD and LH and in mixed histiocytosis, with clinical implications for the therapeutic management of these patients [17] [18].

Table 1. Histopathological findings.

	ECD	LH
CD68	+	+
CD163	+	+
CD1a	−	+
CD207	−	+
S100	+ or −	+
XIIIa	+	−
Touton Giant Cells	+	−
Other characteristic findings of hystiocits	Xanthomatous fibrosis	Birbeck Granules

Adapted from: Diamond EL *et al.* Consensus guidelines for the diagnosis and clinical management of ErdheimChester disease. Blood. 2014.

The treatment of mixed histiocytosis is still a challenge. The most commonly used therapy is Interferon alfa, although it has low efficacy. In patients with a positive test for the BRAFV600E mutation, specific therapy with BRAF inhibitors such as vemurafenib can be considered [19].

Due to the sensitivity of the PET scan for investigating extra-osseous disease in DEC, PET-FDG has become the exam of choice in nuclear medicine, for initial evaluation and follow-up of these patients, which must be performed at intervals from 3 to 6 months, or at longer intervals if disease is stable. There are no specific serum markers for monitoring disease activity; C-reactive protein is elevated in 80% of cases at diagnosis and monitoring its level can be useful in follow-up.

It is currently recommended that treatment should be continued indefinitely as long as tolerated. The decision to wean from medication must be made on a case-by-case basis when the disease is minimal or stable for a prolonged period. BRAF inhibitors increase the risk of accelerating premalignant lesions mediated by the RAS oncogene. Despite this risk, there is no definition of a safe continuous treatment period with vemurafenib in ECD.

Although there are several therapies available, survival in patients who develop the simultaneous occurrence of ECD and LH is significantly lower. The prognosis of these patients is variable and depends on the extent and distribution of the disease, with a 5-year survival rate of 68%. Causes of mortality include pulmonary infection, myocardial infarction, digestive hemorrhage and metabolic disorders, in addition to multiple organ failure [20] [21].

4. Conclusions

The multisystemic involvement of mixed histiocytosis makes diagnosis difficult at first due to its clinical spectrum of overlapping two uncommon pathologies. In our case, the predominant condition was Erdheim-Chester Disease, in which

bone involvement was characteristic. The respiratory symptoms were non-specific and refractory to conventional treatments, which motivated the investigation with complementary tests that led to the clinical diagnosis of ECD, but with an immunohistochemical finding compatible with Langerhans Histiocytosis, configuring an overlap syndrome.

As shown in a literature review, survival in cases of mixed histiocytosis is lower than in isolated histiocytosis and presents limited therapeutic options. The use of immunobiologicals has shown promise, but it still requires more genetic and molecular studies that can guide effective therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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