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Orbital histiocytosis with systemic involvement: A case with complex affiliations

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Abstract:

A 70-year-old male presented with orbital masses affecting the muscular cone. His past medical history was notable for diabetes mellitus, ischemic cardiopathy, sleep-apnea syndrome, and multiple serous effusions. The first biopsy specimen of affected orbital tissue revealed fibrohistiocytic infiltration resembling xanthogranuloma or Erdheim–Chester disease (ECD). An ulterior biopsy of affected orbital tissue showed lymphocyte emperipolesis with immunopositivity for CD68 and S100 but negative staining for CD1a marker, strongly suggesting Rosai–Dorfman disease (RDD). Afterward, pericardium and peritoneal effusions resulted in constrictive pericarditis and retroperitoneal fibrosis, respectively. The absence of distinctive clinical features made the diagnosis especially challenging. Attempts to control the disease using corticosteroids, radiation, orbital surgery, and interferon were unsuccessful. Aggressive treatments such as chemotherapy were not considered appropriate due to the general deterioration of our patient. Although the possibility of two concurrent diseases (e.g., systemic ECD and orbital RDD) cannot be discarded, we interpreted the orbital findings as likely due to RDD, and the entire condition of our patient as an extranodal RDD with atypical clinicopathological findings and outcome.

Keywords:

Erdheim–Chester disease, Non-Langerhans cell histiocytosis, orbital histiocytosis, Rosai–Dorfman disease, systemic histiocytosis

Introduction

Erdheim–Chester disease (ECD) is a rare condition characterized by histiocytic clonal proliferation. Such histiocytes are usually described as having foamy cytoplasm and showing immunopositivity for CD68 and CD163, but negative CD1a and negative S100 immunostaining. They are accompanied by lymphocytes and Touton giant cells.[1] Skeletal involvement consists of osteosclerotic lesions affecting the long bones of the lower limbs bilaterally and is present in 95% of cases.[2] The detection of BRAF V600E mutation in the affected tissue is a distinctive trait.[3]

On the other hand, Rosai–Dorfman disease (RDD) is defined as a benign proliferation of histiocytes with large nucleus and large eosinophilic cytoplasm. They stain positively with CD68 and S100 but do not stain with CD1a. It also demonstrates the variable frequency of the emperipolesis phenomenon.[4]

This entity is somehow heterogeneous and can occur in association with autoimmune, hereditary, and malignant diseases.[5]

Classically, RDD presents with paranasal sinus involvement and giant cervical lymphadenopathy.

Such cases can be designated by the equivalent expression "sinus histiocytosis with massive lymphadenopathy." However, the primary involvement of extranodal sites takes place in 45% of affected patients and on these occasions, the eponymous term is preferred.[6]

The clinical course of RDD has been described as self-limiting, with rare recurrences after surgery. Still, some cases have required more aggressive treatment.[7]

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The clinical and pathological spectrum of both entities displays subtle frontiers, almost overlapping.

This article describes difficulties in the diagnosis and management of a patient suffering from an unusual form of orbital histiocytosis with systemic manifestations, that was finally interpreted as an extranodal RDD.

Case Report

A 70-year-old male was referred urgently to our ophthalmology service by his primary care physician at the end of March 2016 due to exophthalmus, pain, and visual impairment which mostly affected his right eye.

His past medical history was relevant for smoking addiction, increased blood pressure, type 2 diabetes mellitus, hypercholesterolemia, primary hypothyroidism, sleep-apnea syndrome, ischemic cardiopathy, and tramadol allergy. He denied having any history of asthma.

He was also suffering from multiple serous effusions. An abdominal subcutaneous fat needle aspiration biopsy was done, which did not reveal any amyloid material. A pericardial puncture was also done, which was negative for malignant cells. His family history was not remarkable. On examination, his visual acuity was 20/50 in the right eye and 20/30 in the left.Proptosis with significant resistance to retropulsion was present on both sides, but more evident in his right eye. The result of a Goldmann applanation was 18 mmHg. No signs of uveitis or diabetic retinopathy were present. Computed tomography scan (CT) of the orbits revealed infiltrative orbital bilateral masses affecting the intraconal retrobulbar space, larger on the right side, with obliteration of normal fat planes between lesions and all neighboring orbital structures [Figure 1].

Surgical biopsy performed at the IMO ophthalmology center, and subsequent histologic study, carried out at Dexeus University Hospital (Barcelona), revealed fibrohistiocytic infiltration similar to xanthogranuloma, which contained histiocytic cells of various sizes, foamy cytoplasm, and Touton giant cells. Immunophenotype studies were not performed on this sample.

The patient was treated initially with intravenous pulses of 500 mg methylprednisolone weekly, and thereafter with radiation (30 Gy) along with oral and periocular corticosteroid. The volumetric modulated arc therapy radiation technique was used because of its greatly improved delivery efficiency.[8] All these attempts at corticosteroid treatment had to be interrupted prematurely because they were not well tolerated. At the time, there was no improvement of proptosis or relief of pain.

A consultation with the internal medicine department was requested due to suspicion of ECD. Their initial workup consisted of blood tests for auto-immune disorders, IgG4 levels, tumor biomarkers, serological studies for virus (including HIV), repeated head, chest, and abdominal computed tomography (CT) scans, bone scintigraphy, and positron emission tomography (PET-CT). Laboratory results were not relevant to diagnostic guidance.

Chest cavity CT images demonstrated pericardial effusion, as well as delicate spine-like tracts of soft density tissue located in mediastinal fat. Fibrous density changes were also found in subepicardial fat surrounding the right coronary artery and distorting the right atrium. Pleural effusion, pulmonary nodules, and thickening of interlobular septum were also shown.

Abdominal CT scans revealed peritoneal effusion with spine-like tracts of retroperitoneal fat at the major omentum and enclosing the kidneys. Such images evoked the "hairy kidney" described classically in ECD[9] [Figure 2] and showed moderate radiotracer uptake when explored with PET-TC.

These features were temporarily considered consistent with ECD.

Unrelieved right periocular pain led to debulking tumor surgery that was performed at the IMO center.

Surgeon (RM) found an extensive tumor infiltration of adjacent intraorbital structures without a clear dissection plane.

The analysis of the tissue from the tumor specimen revealed a nodular pattern. Nodules contained big histiocytic cells with foamy cytoplasm and oval nucleus, some of them showing lymphocyte emperipolesis. Nodules were delimited by thin fibrous strands. Neither necrotic areas nor mitosis frames were detected.

Immunohistochemically, histiocytes displayed positive staining of CD68, CD4, XIIIa factor, and S100 and negative staining of CD1a, CD30, and Langherine [Figure 3]. This histologic and immunochemical pattern was considered compatible with RDD.

In addition, the patient underwent a bone marrow biopsy. The analysis showed mild myelomonocytic central hypercellularity. Molecular biology failed to demonstrate BRAF mutations and myelodysplastic syndrome markers (JAK, Calreticulin, MPL).

The patient refused a peritoneum and pericardial biopsy. The Internal Medicine Department started treatment with parenteral peginterferon alfa 2A at the beginning of 2017. However, this medication had to be stopped prematurely due to an increase in hepatic enzymes, sickness, and vomiting.

The general condition of the patient worsened slowly. Constrictive pericarditis and chronic renal insufficiency appeared. Ocular motility impairment continued, mostly affecting supraduction, abduction, and adduction of the right eye. Simultaneously, visual acuity of the right eye decreased to light perception, and to 20/40 in the left eye. Proptosis recurred after surgery of the right eye, but later on, it remained steady. TC images confirmed the recurrence of orbital infiltration on the right side, reaching preoperative levels, together with stabilization on the left side. Concomitant uveitis was never assessed.

Considering his deteriorating clinical status, our patient could only be managed with low-dose oral corticosteroid.

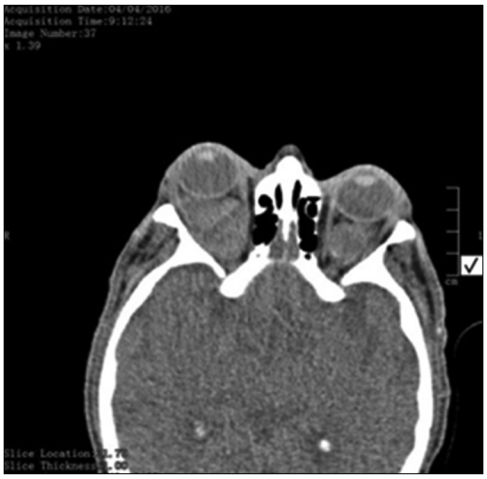

Figure 1: Infiltrative orbital bilateral masses affecting the intraconal retrobulbar space, larger on the right side

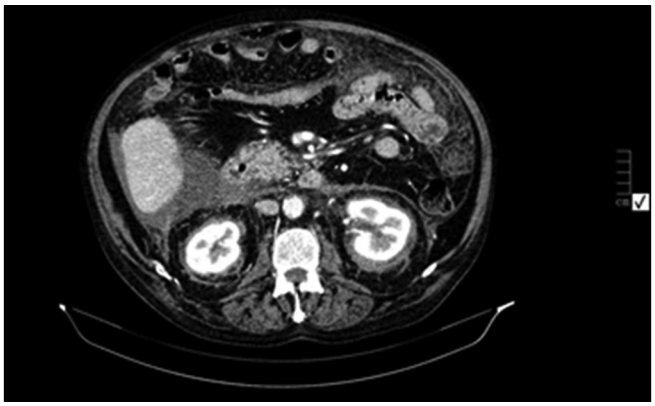

Figure 2: Abdominal computed tomography scans revealed peritoneal effusion, with spine-like tracts of retroperitoneal fat at the major omentum and enclosing kidneys

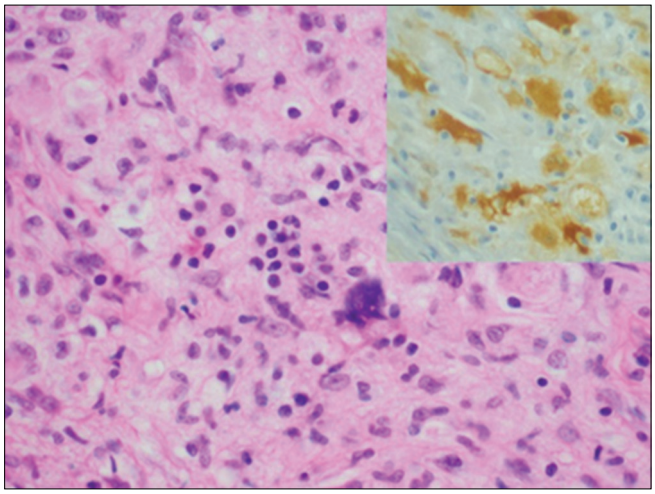

Figure 3: Histiocytic proliferation, emperipolesis; and immunostaining displaying histiocytic expression of S100 (upper right corner of the figure) (H and E)

Finally, the patient died due to cardiorespiratory complications 20 months after initial ocular symptoms. The family denied permission to do an autopsy.

Discussion

Until 1987, ECD and RDD were classified as "non-Langerhans cell histiocytosis." Nevertheless, the latest Histiocyte Society classification does not recognize non-Langerhans cell histiocytosis as a major category. Currently, ECD has become a subset of L group histiocytosis that also includes extracutaneous juvenile xanthogranuloma (nearly a synonym of ECD) and Langerhans cell histiocytosis. On the other hand, different forms of extracutaneous RDD, including extranodal RDD and RDD associated with ECD, currently belong to the R group histiocytosis.[3,9]

The diagnosis and treatment of orbital histiocytosis associated with systemic disorders is always complex or even challenging and usually involves a team effort by multiple medical specialists and dauntless work that does not always reach the desired endpoint.

Neither distinct clinical findings of ECD nor those of RDD (respectively skeletal involvement and massive lymphadenopathy) were present in our patient. Therefore, they could not guide our diagnostic process.

The first anatomopathological evaluation, performed at an outside facility, displayed a xanthogranulomatous disease with foamy histiocytes and Touton-like cells. Consequently, we suspected the patient was suffering from orbital xanthogranuloma (similar to extracutaneous juvenile xanthogranuloma, but limited to the orbit), extracutaneous juvenile xanthogranuloma (JXG) itself, or ECD. The clinical picture of our patient did not accurately fit with either orbital xanthogranuloma or ECD. As a result, at first, our patient was given nonspecific treatments supposedly effective at least for xanthogranulomas, such as systemic corticosteroids and radiation.[10,11]

The lack of response led to an extensive cytoreduction surgery and to new histologic findings (lymphocyte emperipolesis with immunopositivity for CD68 and S100, but negative staining for CD1a marker) that strongly suggested the diagnosis of RDD to our pathologist.

At this point in time, we should remark that neither foamy histiocytes nor "Touton-like" multinucleated cells are distinctive markers for ECD and have also been described previously in RDD.[9,12] Moreover, although our case did not present with diffuse, but restricted emperipolesis, this finding is known to be less conspicuous in extranodal forms of RDD.[9]

The clinical outcome was not stable. Consequently, the patient was treated with pegylated interferon-alpha 2A. Interferon has previously been assayed for the treatment of ECD as well as RDD.[13] Unfortunately, our patient had to stop treatment due to adverse effects.

Chemotherapeutic approaches have also been used to treat both diseases,[4,7] but they could not be assayed in this particular case because of the general status of the patient.

As previously mentioned, extracutaneous JXG was also included in our differential diagnosis. Histopathology and immunophenotype of this entity are not significantly different from ECD[9] and at present, both are included in the same group of histiocytosis. Thus, cells are nonreactive for S-100 protein. However, tissue specimens obtained from our case presented a strong S100 staining.

The main clinical differences between JXG and ECD concern the vital prognosis and the systems they usually involve.

Extracutaneous JXG has been reported to affect the orbital cone in elderly patients,[14] but difficult control of progression is rare in JXG, and so are pericardial and peritoneal involvement when considering extracutaneous forms.[11]

As seen in the preceding paragraphs, this case was especially puzzling to both clinical and morphological science specialists:

The major differential diagnosis in our case included RDD and ECD. Nevertheless, these entities are not always reciprocally exclusive[1,9] and may overlap or coexist.[5,15] This represents a proof that different types of histiocytosis share a common progenitor.[9]

Table 1 summarizes clinical and histologic findings we considered for a differential diagnosis between ECD and RDD.

ECD patients are middle-aged to elderly, ranging from 40 to 80 years. The disease shows a definite predilection for males. Extraskeletal forms of ECD only occur in <5% of patients.[9] Considered on the whole, patients suffering from ECD have mostly neurological (45%), cardiovascular (75%), retroperitoneal (30%), and pulmonary involvement (50%).[2,15,16]

Orbit involvement occurs in nearly 25% of total patients.[15] A poor response and continued progression after surgical debulking or orbital decompression has been described.[17] Our patient exhibited consistent features.

Otherwise, RDD has been reported to present as late as the eighth decade, although the average age of onset is 20 years. Eleven percent of patients have ophthalmic findings, most commonly an orbital mass.[18]

Table 1: Summary of clinical and histologic findings of our patient considered to support the diagnosis of Erdheim-Chester disease or Rosai-Dorfman disease

Findings supporting ECD diagnostic	Findings supporting RDD diagnostic
CD68+, Factor XIIIa+	CD68+, S100+
CD1a−, Langherine−	CD1a−, Langherine−
Touton cells, foamy histiocytes	Lymphocyte emperipolesis
Lungs, heart, and peritoneum involvement	Lungs, heart, and peritoneum involvement
Infiltration of perinephric tissue	Foamy histiocytes, multinucleated cells
Devastating ocular and systemic outcome	

Observe that some of them are shared by both entities and resulted noncontributory for differential diagnosis. ECD=Erdheim-Chester disease; RDD=Rosai-Dorfman disease

Systemic involvement, in cases of orbital RDD, has previously been reported to affect lymph nodes, parotid gland, lungs, and brain.[19] In addition, the heart,[1] bone, skin, upper respiratory tract, palate, testicle, retroperitoneum, and digestive and nervous systems should be mentioned if all extranodal sites are considered.[5,6] Although the disease is usually self-limiting, patients may suffer relapses and perish due to vital organ compression.[4]

Our case provides, to the best of our knowledge, a singular condition with simultaneous orbital, pulmonary, retroperitoneal, and cardiac manifestations somehow associated with RDD.

We would like to remark that, before writing this report, histologic slides from initial and second biopsy specimens were revisited and compared by both pathology teams from our hospital and Dexeus University Hospital. They concluded that findings from both specimens were similar and from a morphological standpoint, consistent with the diagnosis of RDD.

In conclusion, nonconforming cases of RDD depict misleading boundaries with ECD. A differential diagnosis can be troublesome if neither clinical nor histologically distinctive findings are present and the patient's general status prevents further examinations or therapeutic trials from taking place.

In this particular case, a definitive or complete diagnosis could not be achieved, but according to available data (especially a congruous immunophenotype), the authors contend that affiliation of the disease is closer to extranodal RRD. Nevertheless, the presence of atypical clinical (pleural and peritoneal findings) and histological (foamy histiocytes and Touton-like cells) manifestations are noticeable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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