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Rosai - Dorfman disease: a rare entity diagnosed at autopsy

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ABSTRACT

Rosai-Dorfman disease (RDD) or Sinus histiocytosis with massive lymphadenopathy is a rare and benign histiocytic proliferative disorder first described by Juan Rosai and Ronald Dorfman in 1969, whose etiology remains unknown. Since then, many cases were reported in the literature. The disease primarily involves the lymph nodes, and is characterized by painless, bilateral cervical lymphadenopathy accompanied by fever, night sweats, malaise and weight loss, reason why many patients are clinically misdiagnosed as malignant lymphoma. In some cases, extranodal involvement may be present. Leukocytosis, elevated erythrocyte sedimentation rate, and hypergamaglobulinemia are often present. The authors report a case of a 52-year-old female patient admitted to the hospital with the diagnosis of pneumonia and progressed to multiple organs failure and death. During the hospitalization an attempt to diagnose a lymphoproliferative disease trough an axillary lymph node biopsy was disappointing. The autopsy was crucial for the diagnosis, illustrating a severe and unusual presentation of Rosai-Dorfman disease.

Keywords: Histiocytosis, Sinus; Emperipolesis; Sepsis; Autopsy.

CASE REPORT

A 52-year-old female patient sought the medical assistance complaining of 6-month history of progressive weight loss of 16kg. More recently she started experiencing thoracic pain followed by pleural effusion, persistent cough and fever. She referred being previously prescribed an antibiotic course without improvement.

Physical examination, at admission, showed an ill-looking patient, pale, dehydrated and febrile (38,2 °C); room air oximetry was 97%. Pulmonary examination revealed crepitation rales in the inferior two thirds of both lungs and the remaining exam was unremarkable. No enlarged lymph nodes were detected. Initial laboratory work up is shown in Table 1.

The patient was hospitalized with the diagnosis of pneumonia and antibiotic therapy was promptly started. Clinical outcome was unfavorable progressing with hypotension, respiratory failure, acute renal failure, thrombocytopenia and liver dysfunction, requiring mechanical ventilatory support, intravenous vasoactive drugs and hemodialysis. The β-2 microglobulin determination was 16.5 µg/mL (RV, 1.0-1.7 µg/mL).

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Table 1 – Initial laboratory work up

Exam	Result	RV	Exam	Result	RV
Hemoglobin	9.0	12.3-15.3 g/dL	Platelet	230	150-400 × 10^3/mm^3
Hematocrit	28.2	36.0-45.0%	Creatinine	0,72	0.4-1.3 mg/dL
Leukocytes	17.47	4.4-11.3 × 10^3/mm^3	Urea	24	10-50 mg/dL
Segmented	90.7	46-75%	Sodium	130	136-146 mEq/L
Eosinophil	1.2	1-4%	Potassium	4.4	3.5-5.0 mEq/L
Basophil	0.2	0-2.5%	AST	131	10-31 U/L
Lymphocyte	4.7	18-40%	ALT	46	9-36 U/L
Monocyte	3.2	2-9%	CRP	236	<5,0 mg/dL

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP= C reactive protein ; RV = reference value.

During the hospitalization, an enlarged axillary lymph node was detected and biopsied. The biopsy specimen showed hyperplasia with reactive paracortical pattern associated to focal aggregates of epithelioid histiocytes (CD68+/S100 negative). Additional sections of the paraffin block were analyzed, without contribution to the diagnosis. The patient progressed to neurological dysfunction and coma. The brain magnetic resonance imaging (MRI) showed a hemorrhagic lesion in the right cerebellar hemisphere. The patient did not recover and died after 2 weeks of hospitalization. An autopsy was performed.

Autopsy Findings

The external examination showed an obese patient weighing 81 kg, measuring 167 cm showing signs of anasarca, ischemic necrosis at the tip of the tongue, fingers of the upper and lower limbs.

At the opening of the cavities a generalized lymphadenomegaly was observed. Lymph nodes of the pulmonary hilum, periaortic, pelvic, and axillary were enlarged, measuring up to 1.8 cm. Microscopically, these lymph nodes showed a Castleman-like appearance, with germinal centers of lymphoid follicles replaced by a proliferation of follicular dendritic cells and deposits of amorphous matrix. The paracortical area was expanded and exhibited vascular proliferation, immunoblasts and histiocytic cells presenting intact lymphocytes emperipolesis. The sinuses were filled by these histiocytic cells some of them showing emperipolesis. These cells were histiocytes S-100+/CD68+/CD1a negative (Figure 1).

Gross examination of the pleural cavity disclosed a bilateral, serosanguineaous pleural effusion with 300 mL in each side. The left lung weighed 469 g (RV, 325-480 g), while the right lung weighed 500 g (RV, 360-570 g) and presented a mild friability in the middle and lower lobes. The microscopic examination showed alveolar septa thickening, intraalveolar edema and foci of neutrophils, histiocytes and desquamating pneumocytes. The pericardial sac overture disclosed a 100 mL of yellow-citrine effusion. The heart was normal in size, weighing 360g (RV, 200-350 g) but presented left ventricular hypertrophy with the posterior wall thickness of 2 cm (RV, 1,5 cm).

In the abdominal cavity, the viscera were congested. The liver weighed 2.014 g (VR, 1.400-1.600 g) exhibiting a brownish coloring surface. At cut surface, there were some irregular, poorly defined whitish subcapsular areas, which corresponded to Zahn's infarct. The spleen was congested, enlarged, weighing 400 g (VR, 150 g). On microscopic examination a lymphocytic depletion was evidenced, associated to S-100 and CD68 positive histiocytes showing lymphocytes emperipolesis. Splenic micro infarctions were also noted. Gastrointestinal tract still showed mild hemorrhagic suffusions in the stomach and in the gastro-esophageal transition.

The kidneys were enlarged, weighing 252 g and 292 g, the right and the left respectively (RV, 120-150 g). At cut surface they exhibited a pale cortex, compatible with acute tubular necrosis, confirmed on microscopy. Several bleeding points, compatible with the diagnosis of acute hemorrhagic cystitis, covered bladder mucosa.

The pelvic gross examination disclosed the absence of the uterus; a paraanexial hematoma measuring 8.0 × 7.0 cm on the right, a paratubarian cyst and atrophic ovaries.

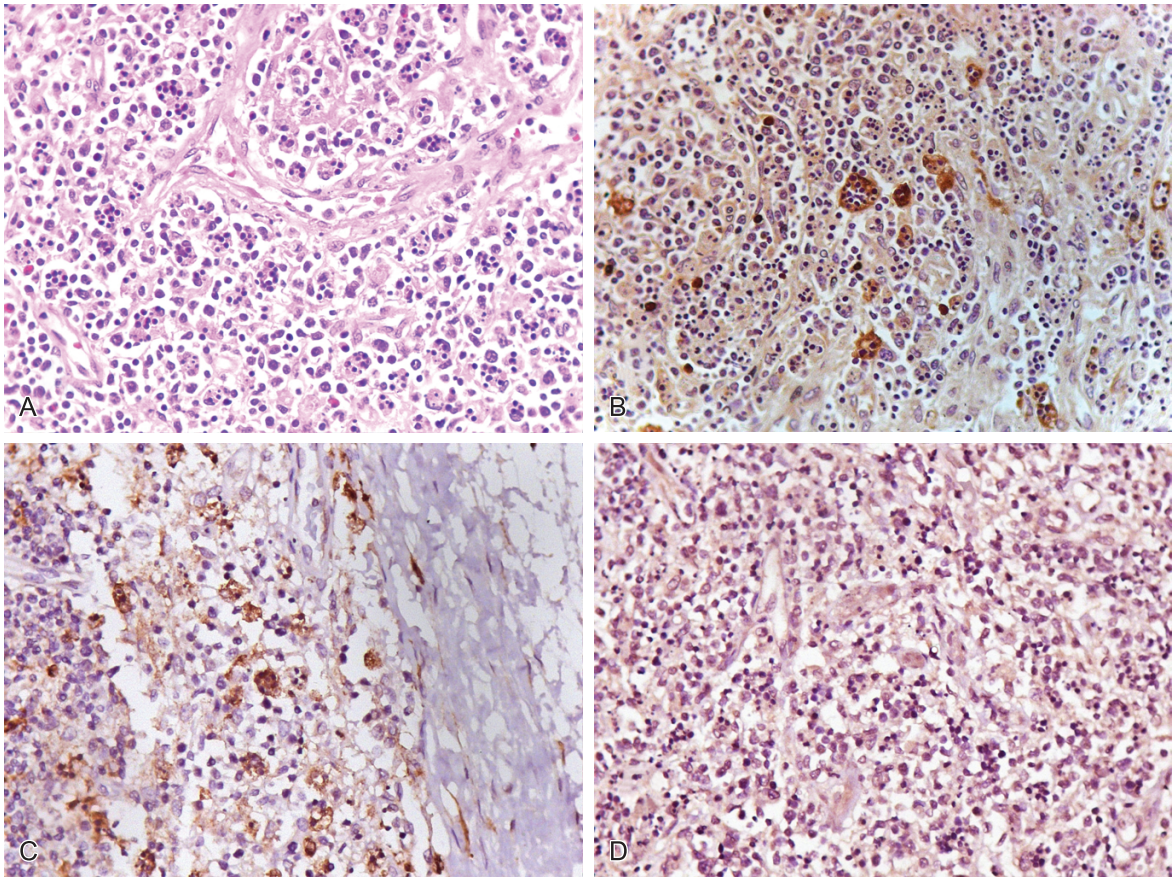

Figure 1 – Photomicrography of the lymph node showing in **A** - Histiocytic cells showing emperipolesis (H&E 40×); **B** - Histiocytic cells S-100+ (40×); **C** - Histiocytic cells CD68+ (40×); **D** - Histiocytic cells CD1a negative (40×).

The bone marrow was hypercellular, represented by 70% of hematopoietic cells, mainly at the expense of the granulocytic series. S-100+ and CD68+ histiocytes with emperipolesis were present, but in small number (Figure 2).

At the opening of the skull, the brain was congested, weighing 1.226g (VR, 1.200-1.600 g), with an acute right cerebellar hemorrhage, measuring 4.0 × 2.6 cm surrounded by gliosis (Figure 3).

DISCUSSION

Rosai-Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy is a rare, benign, and idiopathic disorder first described by Juan Rosai and Ronald Dorfman in 1969. It is a self-limiting proliferative histiocytic disorder, in which lymphadenopathy results from infiltration and dilatation of the lymph node sinuses by large foamy histiocytes which engulf intact lymphocytes and/or plasma cells within their cytoplasm, phenomenon known as emperipolesis.[1-3] Emperipolesis is considered the most remarkable feature in Rosai-Dorfman Disease, but may occur in other diseases such as H syndrome, carcinoma, neuroblastoma, multiple myeloma, leukemia, autoimmune hemolytic anemia, and malignant lymphomas (rarely).[4-10]

The disease affects any age group but occurs mainly in the first two decades of life. Men are slightly more affected (58%) than women and this predominance is highly observed among the African descendents. The most frequent clinical presentation (in 95% of cases) is a massive bilateral and painless cervical lymphadenopathy. Other symptoms include fever, night sweats, malaise and weight loss. Leukocytosis, elevated erythrocyte sedimentation rate and hypergamaglobulinemia, are frequent laboratory alterations.[1-3,11]

Although it has been investigated for over the last 20 years, the etiology remains fully uncertain. There are some theories that try to correlate the disease with an undefined reactive process or an immune defect triggered by a viral infection, namely: human herpes virus type 6 (HHV6), Epstein Barr virus (EBV) or cytomegalovirus (CMV).[2,3,9,12]

Although the most common presentation of the disease is represented by the involvement of

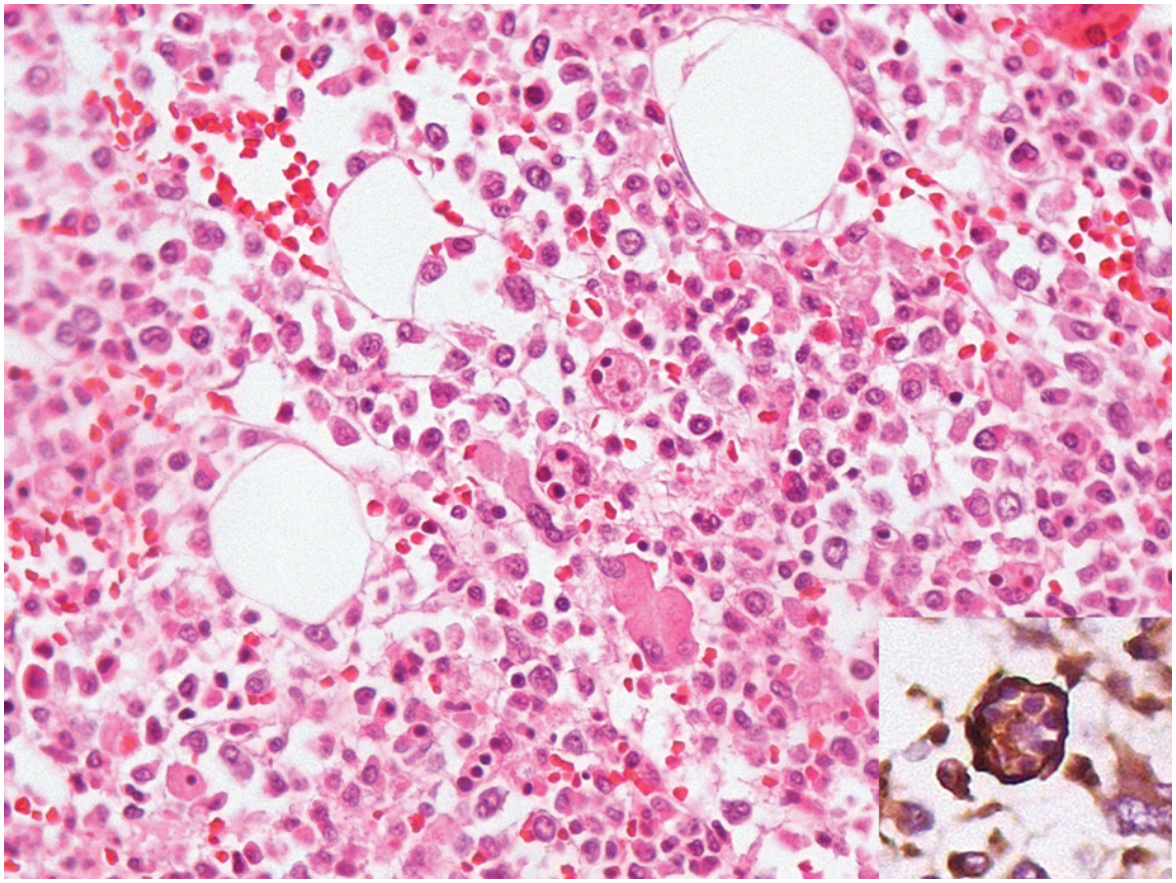

Figure 2 – Photomicrography of the bone marrow showing emperipolesis (H&E 40×) (note the enlarged picture on the left bottom depicting a histiocyte CD68+ with emperipolesis.

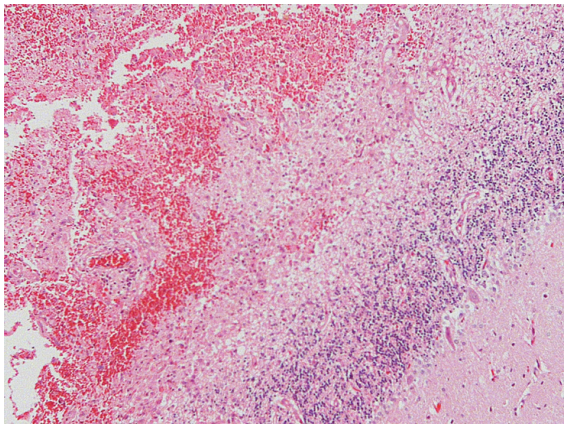

Figure 3 – Photomicrography of the cerebellum showing acute cerebellar hemorrhage and gliosis (H&E 10×).

peripheral or central (mediastinal or retroperitoneal) lymph nodes, extranodal involvement may also be observed, such as the skin, head and neck, breast, brain, gastrointestinal tract, respiratory tract, and orbit. The simultaneous involvement of lymph nodes and extranodal sites occurs in 43% of cases while isolated involvement of extranodal sites occurs in 23% of cases.[1-4]

Lymph node biopsy is the cornerstone for the diagnosis of RDD, which is characterized by the identification of infiltrating pale eosinophilic histiocytes demonstrating emperipolesis and expressing positivity for S-100, CD68, CD163 antigens, while Langherin and CD1a are typically negative. The RDD cells are moderate to large in size, with a large and round nuclei marginated by a pale chromatin. Some researchers attribute its origin to the bone marrow stem cells.[1,3,9,13-16]

There is a relationship between the disease and immune disorders such as rheumatologic diseases (mainly rheumatoid arthritis), asthma, glomerulonephritis and Wiskott-Aldrich syndrome. RDD is also observed in association with hematological autoantibodies. Foucar, Rosai and Dorfman published a study, which examined 14 deaths of patients with RDD and found that the most frequent cause of death in this population was related to a marked impairment in the immune system.[1,2,9,12,15,17,18]

Some differential diagnoses include other histiocytic disorders like Langerhans cell histiocytosis (LCH), hemophagocytic syndrome, and nonspecific sinus hyperplasia. In LCH, the Langerhans cells have a homogeneously stained pink cytoplasm, lobulated nuclei, do not have phagocytic activity and are CD1a positive, besides having Birbeck

granules by electron microscopic. Hemophagocytic syndrome shows hemophagocytosis mainly of red cells, absence of emperipolesis, and the presence of pancytopenia and hepatosplenomegaly. In reactive sinus hyperplasia emperipolesis is absent. In these two last conditions, the histiocytes are S-100 negative.[1,13,15]

The generalized lymphadenopathy was the major finding of this autopsy case, which immediately caught the attention for the possibility of a lymphoproliferative disorder. However, the microscopic examination of the lymph nodes, showed the pattern of sinus histiocytosis with emperipolesis. This finding was detected on multiple lymph nodes of different chains, mainly those of deep chains. Although this lymph node commitment is not the typical presentation of Rosai-Dorfman disease, it remained the main hypothesis. The immunohistochemical profile of these histiocytes (S-100+/CD68+ and CD1a negative), were conclusive for the final diagnosis.

In addition to the lymph nodes, other sites related to the hematological system showed emperipolesis, such as the spleen and bone marrow featuring extranodal involvement of the disease.

The impairment of the immune system related to RDD appears to have been responsible for the pneumonia and pleural effusion, ending with the septicemia and refractory shock. The prolonged hypotension in conjunction with vasoactive drugs administration and the possible intravascular disseminated coagulopathy were responsible for the splenic micro infarctions, liver ischemic necrosis, acute tubular necrosis, extremity necrosis (tip of the tongue and fingers), as well as the hemorrhagic findings in the pelvis, brain and gastrointestinal mucosae. The cerebellar hemorrhage, much probably was the immediate cause of death.

According to some authors, RDD may show different stages of progression. In many cases, depending on the stage of the disease, the lymph node biopsy may not identify emperipolesis. It is believed that the transformation of monocytes in RDD histiocytes occurs at an early stage and emperipolesis takes some time to emerge. Biopsies performed during this early phase of exacerbation may fail to show emperipolesis and therefore the diagnosis may eventually be compromised. That was observed in this case report, when during hospitalization, the patient underwent an axillary lymph node biopsy, which showed sinus histiocytosis, CD68 positive, and S-100 negative, without emperipolesis.[3]

The clinical behavior of RDD is usually benign or indolent presenting spontaneous regression in the majority of patients. In these cases treatment is unnecessary. But in a few patients the disease behaves progressively requiring treatment. Systemic symptoms, as well as lymph nodes enlargement require corticosteroid therapy. In case of compressive symptoms, surgery and high-dose corticosteroids should be tried. Radiotherapy may be useful as curative or palliative therapy in resistant cases and when surgery is not feasible. Chemotherapy should be restricted to patients with life-threatening disease or in those non-responsive to standard therapy or after multiples relapses.[2,13,18-23]

Although rare, Rosai Dorfman disease should always be included in the differential diagnosis of lymphadenopathy. Despite showing striking diagnostic features, it is important to remember that the biopsy specimen may not contain all the elements needed for a final diagnosis, depending on the stage of the disease. Despite being defined as a disease of benign behavior, it is accompanied by severe immune disorders that may lead to severe infectious which can lead the patient to death.

In this case autopsy was central to this case elucidation, showing once again the valuable contribution of this examination to clarify a seemingly simple case.

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