

History of Rosai-Dorfman Disease

In 1969, Dr. Juan Rosai and Dr. Ronald F. Dorfman reported four cases of an entity that previously had puzzled pathologists and clinicians. The four cases had failed to fit under any diagnosis, but shared a few common characteristics. Each patient presented with painless, massive lymphadenopathy, most commonly of the cervical lymph nodes¹. Other locations included the inguinal, intra-parotid, and axillary lymph nodes. The patients all presented with fever and leukocytosis¹. The differential diagnosis included malignant lymphoma, malignant histiocytosis, reticuloendotheliosis, and chronic inflammation. However, the histopathological characteristics of the cases did not fit the classical characteristics of these diagnoses. Based on the pathologic findings, Dr. Rosai and Dr. Dorfman created a new entity, which they called "sinus histiocytosis with massive lymphadenopathy (SHML)."¹

Pathologic Findings of SHML

The four original cases presented by Dr. Rosai and Dr. Dorfman shared pathologic findings that were the basis for the new entity "sinus histiocytosis with massive lymphadenopathy." The pathologic findings included:

- Marked fibrosis of the lymph node capsule with lymphocyte and plasma cell infiltration¹
- Dilation of the subcapsular and medullary septae¹
- Increased intra-sinus histiocytes with little atypia and few mitoses, and as the disease progresses, histiocyte infiltration of the medullary space¹
- **Emperipolesis**: the presence of viable lymphocytes (most commonly) or red blood cells within the cytoplasm of benign histiocytes was a consistent finding. Cells are commonly within vacuoles, distributed around the periphery of the histiocyte^{1,2}

Rosai-Dorfman Disease

Since 1969, the diagnosis of SHML has been a well-recognized clinical and pathologic entity. SHML involving extra-nodal tissue has been termed Rosai-Dorfman disease (RDD) and is present in 43% of patients³. Common sites of extra-nodal involvement include the skin, upper respiratory tract, eyelid, orbit, bone, salivary glands, and CNS. More recently, additional pathological criteria have been added for the diagnosis of RDD, including specific immunohistochemical stains for activated phagocytes. Characteristically, the histiocytes are S100+ and CD68+, and CD1a-³ confirming a non-Langerhans cell histiocytosis.

Ocular Presentation of Rosai-Dorfman Disease

A 45 year-old African American male presented with a two year history of a slowly enlarging, elevated, fleshy conjunctival nodule in his left eye (OS). The lesion involved the inferotemporal bulbar and forniceal conjunctiva and extended onto the peripheral cornea between 2 and 6 o'clock. The patient had a smaller lesion between 6 and 8 o'clock in his right eye. The differential diagnosis included conjunctival lymphoma, orbital lymphoma, or conjunctival episcleritis.



Figure 1. 45 year-old man with bilateral conjunctival lesions with a differential diagnosis of atypical conjunctival lymphoma and episcleritis. (A/B) Photograph of the raised conjunctival nodule OS showing corneal involvement and ectropion.

Biopsy Findings

Excisional biopsy of the lesion was performed. Microscopic evaluation revealed the following:

- Massive infiltration of histiocytes with pale, eosinophilic, granular cytoplasm, with prominent nuclei and nucleoli
- Emperipolesis: histiocyte phagocytosis of lymphocytes
- No evidence of malignancy (atypia or mitoses)

Flow cytometry revealed no evidence of a clonal B cell proliferation. Immunohistochemistry: Histiocyte markers S100+, CD 68+, CD 138+ Findings were consistent with the diagnosis of Rosai-Dorfman Disease

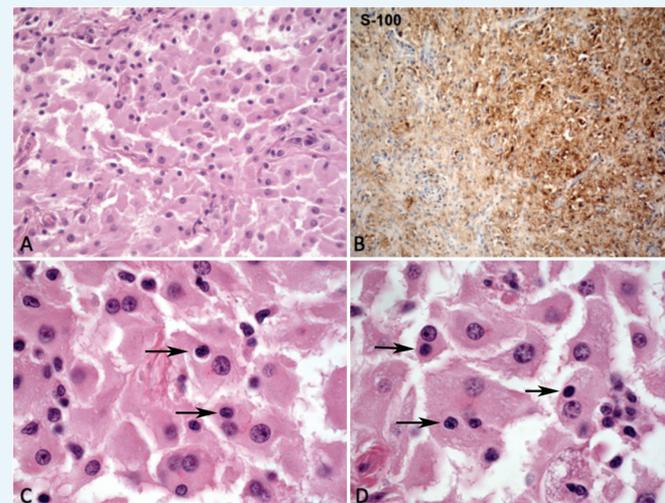


Figure 2. Histopathology of the conjunctival lesion. (A) Infiltrate of histiocytes with copious granular, eosinophilic cytoplasm (B) Histiocytes are immunoreactive for S-100. (C/D) Arrows denote emperipolesis within histiocytes (histiocyte phagocytosis of viable lymphocytes and plasma cells, the signature finding of Rosai-Dorfman disease) A. H&E x100, B. IHC for S-100 x100, C/D. H&E x400

Ocular Manifestations

The case depicts a conjunctival tumor that proved to be Rosai-Dorfman disease (RDD) on pathologic examination. Ocular manifestations of Rosai-Dorfman Disease occur in 10-11% of cases³. Most commonly, it manifests in the orbit, presenting as a mass causing proptosis of the eye³ or as an eyelid tumor. Rarely, RDD involves the ocular surface as an epibulbar tumor⁴ as in this case, or arises intra-ocularly, where it may simulate a choroidal melanoma⁵. In such extra-nodal cases, diagnosis rests on the characteristic microscopic appearance and immunoreactivity of the histiocytic cells. Although RDD is rare, ocular and ocular adnexal involvement is not an uncommon presentation, and the disorder should be included in the differential diagnosis of conjunctival and eyelid lesions. This patient was treated with surgical excision. There currently is no standard protocol for the treatment of ocular RDD.

Conclusion

In 1969, Dr. Rosai and Dr. Dorfman described a new entity, sinus histiocytosis with massive lymphadenopathy. The classic pathologic features include emperipolesis and S-100+ histiocytosis. Since 1969, similar pathologic features have been found in extra-nodal sites in patients without lymph node involvement. The term Rosai-Dorfman disease includes both nodal disease (SHML) and extra-nodal disease. The etiology of RDD is unknown and treatment is not well established. RDD is a benign condition that remains stable in 54% of cases, spontaneously regresses in 21% and progresses in only 1%.³

References

1. Rosai J, Dorfman RF: Sinus Histiocytosis with massive lymphadenopathy. A newly recognized benign clinicopathological entity. *Arch Pathol* 1969, 87:63-70.
2. Rosai J, Dorfman RF: Sinus Histiocytosis with massive lymphadenopathy: a pseudolymphomatous benign disorder. Analysis of 34 cases. *Cancer* 1972, 30:1174
3. Foucar E, Rosai J, Dorfman RF: Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) Review of the entity. *Semin Diagn Pathol* 1990, 7(1): 19-73.
4. Zimmerman LE, Hidayat AA, Grantham RL, Chavis RM, Stopak SS, Dreizen NG, O'Neill JF: Atypical Cases of sinus histiocytosis (Rosai-Dorfman disease) with ophthalmological manifestation. *Trans Am Ophthalmol Soc* 1988, 86:113-135
5. Vermeulen TL, Isaacs TW, Spagnolo D, Amanuel B: Rosai-Dorfman disease presenting as choroidal melanoma: a case report and review of the literature. *Graefes Arch Clin Exp Ophthalmol* 2013, 251:295-299