Case Report

Extranodal Rosai-Dorfman Disease in the Left Bulbar Conjunctiva: A Rare Case Report

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Rosai-Dorfman disease (RDD) is a non-Langerhans histiocytosis characterized by accumulation of S100-positive foamy histiocytes, frequently demonstrating emperipolesis within lymph nodes or extranodal tissues. Extranodal disease is reported in 43% of cases. We present a case of a healthy 11-year-old male with a non-mobile, rapidly enlarging 1.5 cm mass in the medial canthal area of his left superonasal bulbar conjunctiva, and a 3.5 cm firm rubbery left neck mass. The patient denied any eye, neck, or weight loss symptoms. CMV, EBV, and bartonella antibody tested negative. Imaging report was noncontributory. Flow cytometry showed no evidence of lymphoproliferative neoplasm. The left conjunctival excision revealed histiocytic disorder of non-Langerhans cell type with xanthomatous changes. Immunostains showed positive CD20, PAX5, CD3, S100, CD68, CD163, FXIIIA, lysozyme, and fascin. Immunostains for CD1a, BRAF V600E, and ALK-1 were negative. It was clinically indeterminate whether the two masses involved an intraorbital malignant process with metastatic disease to the cervical lymph nodes, Hodgkin lymphoma, or an infectious etiology. In addition, S100 positivity is nonreactive in most cases of juvenile xanthogranuloma and does not rule out the diagnosis. Lymph node resection confirmed sinus histiocytosis with massive lymphadenopathy favoring RDD, histologically consistent with the conjunctival mass.

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INTRODUCTION

Rosai-Dorfman disease (RDD) is a non-Langerhans histiocytosis characterized by accumulation of S100-positive histiocytes, frequently demonstrating emperipolesis, within lymph nodes or extranodal tissues.[1] Extranodal disease is reported in 43% of cases where ophthalmic manifestations occur in 10% of cases.[1,2] Most nodal RDD occurs in the 2nd and 3rd decades whereas extranodal RDD appears in the 5th decade of life.[1] Patients typically presents with painless, slow-growing cervical lymphadenopathy and associated fever, night sweats, and weight loss.[1,2,3,4] Primary ophthalmic RDD is extremely rare and often diagnosed after pathologic studies are performed.[1,3] We present an unusual case of rare extranodal ophthalmic RDD (sinus histiocytosis and massive lymphadenopathy) in a healthy 11-year-old male.

CASE PRESENTATION

An 11-year-old male with no significant past medical history presented with a non-mobile, rapidly enlarging 1.5 cm mass in the medial canthal area of his left supranasal bulbar conjunctiva, and a painless 3.5 cm firm rubbery left neck mass. The patient denied any vision changes, proptosis, nystagmus, restricted range of motion of the eye or neck, fever, chills, or unintentional weight loss. CMV, EBV and Bartonella antibody tested negative. Ultrasound and CT showed two enlarged cervical lymph nodes in the left submandibular region. Chest X-ray was negative for pulmonary masses. The patient was referred to ophthalmology for surgical biopsy.

On microscopy, the left conjunctival excision revealed histiocytic disorder of non-Langerhans cell type with xanthomatous changes and mitoses (**Figures 1A and 1B**). No microorganisms were identified by Ziehl-Neelsen and GMS stains. Immunohistochemistry of the histiocytes stained positive for S100 (**Figure 1C**), CD68, CD163, Factor XIIIa, lysozyme (**Figure 1D**), and fascin, while negative for CD1a. Flow cytometry reported no definite evidence of a lymphoproliferative neoplasm or acute leukemia. The patient's case was presented to the multidisciplinary tumor board recommending left lymph node resection to determine multifocal histiocytosis or primary lymphoma of the left neck.

A lymph node core biopsy and subsequent resection show nodal architecture altered by markedly widened sinuses (**Figure 2A**). On high power view, multiple clusters of histiocytes with abundant foamy cytoplasm, histiocytes with

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emperipolesis of small lymphocytes (**Figure 2B**), and increased scattered eosinophils, plasma cells, and few neutrophils are identified. Definite Hodgkin cells were not identified on H&E. Immunohistochemistry stains performed showed the large histiocytes positive for CD68, CD163, S100 (**Figure 2C**), lysozyme, and OCT2. Immunohistochemistry stains for CD1a, BRAF V600E, and ALK-1 were negative for histiocytes. CD20/PAX5 highlighted positive B-cells present in follicles. CD3/CD5 highlighted positive T-cells present in the interfollicular areas. CD21/CD23 highlighted follicular dendritic cell meshwork. CD15 stained positive for neutrophils, and CD30 showed rare scattered immunoblasts. MIB-1 highlighted the benign germinal centers. Concurrent flow cytometry reported no evidence of lymphoproliferative B-cell neoplasm.

The final diagnosis was extranodal and nodal Rosai Dorfman disease (sinus histiocytosis with massive lymphadenopathy) of the left conjunctiva and left neck. The patient had no further complications on follow-up visits.

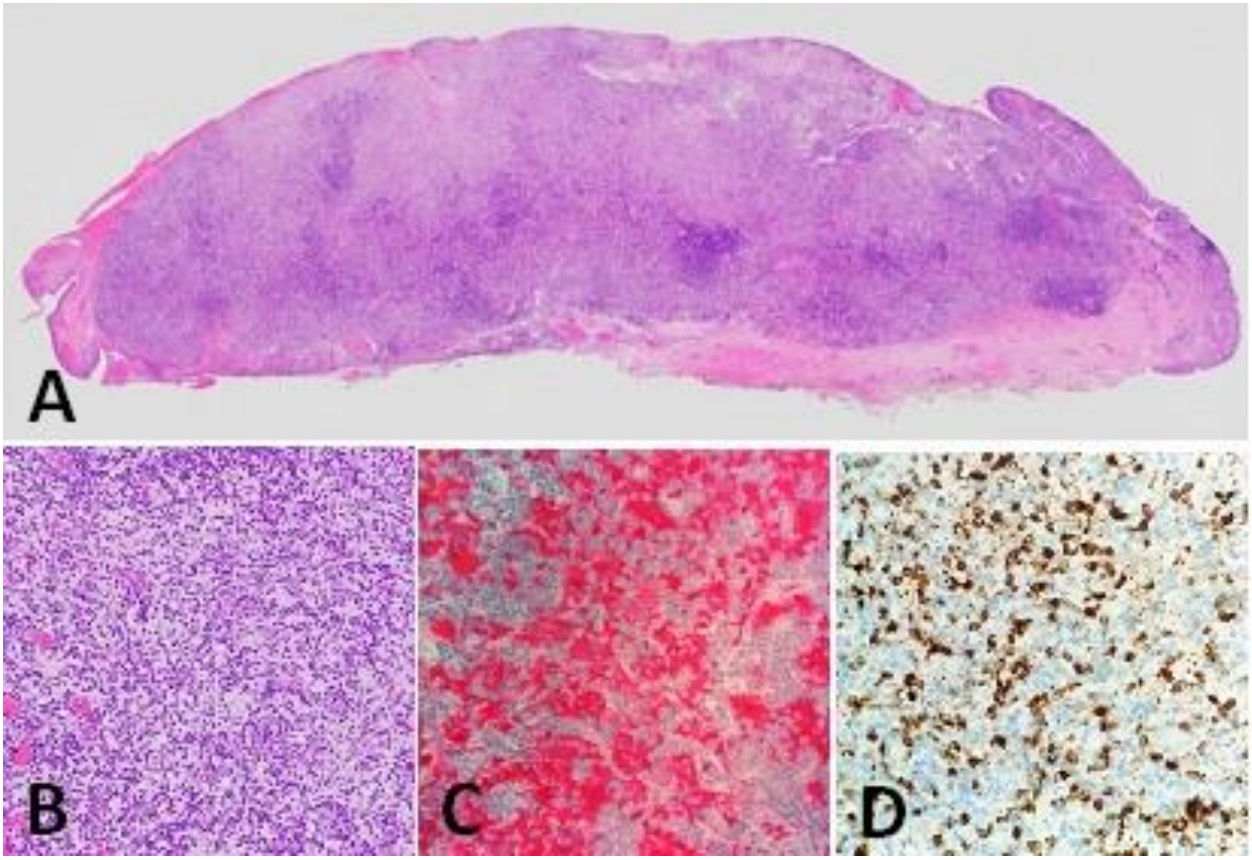

Figure 1. A) Conjunctiva, 20x. **B)** Histiocytes in a background of lymphocytes, eosinophils, and plasma cells, 200x. **C)** S100, 400x. **D)** Lysozyme, 400x.

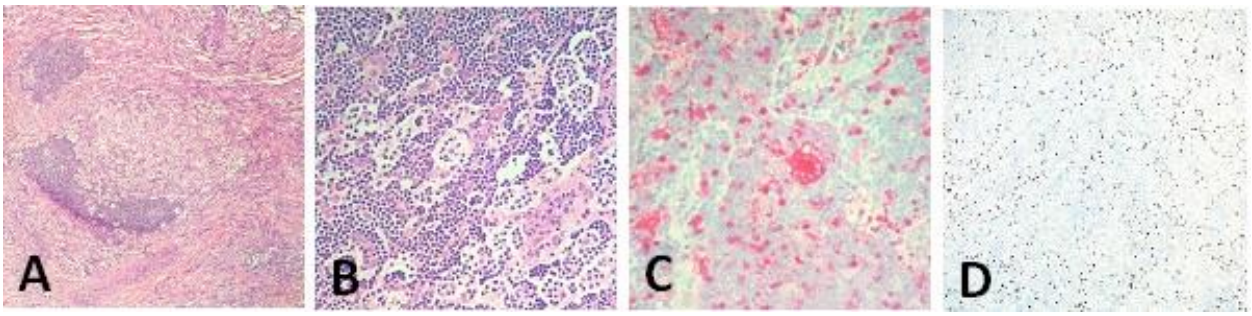

Figure 2. A) Clusters of histiocytes within a lymph node, 40x. **B**) Emperipolesis, 200x. **C**) S100, 400x. **D**) Ki-67, 40x.

DISCUSSION

This case was clinically indeterminate whether the two masses consisted of an intraorbital malignant process with metastatic disease to the cervical lymph nodes, lymphoproliferative disorder such as follicular hyperplasia, or an infectious etiology. The leading diagnosis was lymphocytic predominant Hodgkin lymphoma, given the nodes were firm, mobile and unilateral. However, the eye mass that was simultaneously noted during progression of the enlarging submandibular mass did not appear to be a lymphoproliferative disorder. The histologic specimen predominantly showed large histiocytes with features of emperipolesis and immunoreactivity to S100 in a background of lymphocytes, eosinophils, plasma cells, and scattered neutrophils favoring a diagnosis of RDD. An infectious etiology was also unlikely given that the patient had no recent history of infection, no fever, no overlying skin changes, and no positive antibody tests. Repeat biopsies were not recommended as the sample may not be representative of the underlying pathology.[5] Surgical excision and pathologic studies typically confirm the diagnosis.[5]

There are varying manifestations of RDD including classic nodal RDD, extranodal RDD, neoplasia-related RDD, immune-related RDD, and familial RDD.[1] Classic nodal RDD involves the cervical lymph nodes followed by inguinal, axillary, and mediastinal lymph nodes.[1,2,6] Extra nodal RDD involves the nasal cavity, paranasal sinuses, salivary gland, skin, soft tissue, upper respiratory tract, bone, and central nervous system.[3,6] Neoplasia-related RDD is associated with lymphoproliferative neoplasm, leukemia, and histiocytosis; while immune-related RDD is associated with systemic lupus erythematosus, idiopathic juvenile arthritis, autoimmune hemolytic anemia, and HIV.[6] Familial RDD has germline mutations in SLC29A3 (H syndrome/Faisalabad histiocytosis)[3,7] or TNFRSF6 (autoimmune lymphoproliferative syndrome).[2,6]

Extranodal RDD disease is reported in 43% of cases, of which 10% of cases reported ophthalmic manifestations.[1,2] Common ophthalmic symptoms reported include proptosis, reduced vision, restricted motility, ptosis, compressive optic neuropathy, and diplopia.[3] Gross examination of lymph nodes form firm yellow multinodular mass with a fibrotic cut surface.[4] Histologically, the histiocytes are immunoreactive for S100 demonstrating round nucleus, prominent nucleoli, abundant pale cytoplasm often with emperipolesis, and abundant plasma cells in the background.[1,4] Other positive histiocytic immunostain include CD68, CD163, OCT2, P-ERK, and Cyclin D1.[8] Immunostains for CD1a and langerin are negative.[8]

The pathogenesis of RDD is not well understood.[9] Many cases report gain-of-function mutations in the MAPK pathway, particularly KRAS and MAP2K1 mutations.[9,10] Other notable mutations include NRAS, ARAF, CSF1R, and BRAF P.V600E.[11,12] The differential diagnosis includes infectious diseases, IgG4-related disease, Langerhans cell histiocytosis, juvenile xanthogranuloma, and other histiocytosis disorders.[1,4]

CONCLUSION

In conclusion, this is a rare case of extranodal RDD presenting with unusual clinical manifestation and uncommon site localization in a healthy 11-year-old male. Primary ophthalmic or orbital involvement is often suspected to be lymphoma. Without systemic symptoms, histopathologic and immunohistochemical analysis was critical for establishing the diagnosis. The presence of emperipolesis on histology is a characterizing feature of classic RDD. Other diagnostic examination included careful clinical history review, assessment of disease extent by imaging, histopathology, ancillary studies, and evaluation for conditions associated with RDD. Many cases of RDD can be managed with observation alone, whereas other patients require a variety of therapeutic agents. Multidisciplinary collaboration is often vital.

Disclosure: The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript. All procedures in the study involving human participants were in accordance with the institution's ethical standards. No new data were generated or analyzed during this study.

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