

Systemic and Craniospinal Rosai Dorfman Disease with Intraparenchymal, Intramedullary and Leptomeningeal Disease

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ABSTRACT

Rosai Dorfman disease is a rare histiocytic disorder of over-production of non-Langerhans histiocytes, which typically manifests with massive lymphadenopathy and sinonasal involvement. We report a rare case of systemic and disseminated craniospinal Rosai Dorfman disease with intraparenchymal and leptomeningeal involvement, but no sinus or dural-based disease. The diagnosis was established by biopsy of a hypothalamic mass. Additionally, UCSF500 Next Generation Sequencing demonstrated a solitary pathogenic alteration affecting the BRAF oncogene, which supports the morphologic and immunohistochemical diagnosis of Rosai-Dorfman disease.

Keywords: Rosai Dorfman disease; histiocytosis; BRAF

INTRODUCTION

Rosai Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a rare histiocytic disorder that involves the over-production of non-Langerhans histiocytes. The most common, though nonspecific, imaging feature of Rosai Dorfman disease is massive cervical lymphadenopathy¹. Other commonly involved regions of the body include the skin, sinonasal cavity, orbits, bones, salivary glands, and rarely, the central nervous system (CNS). CNS involvement in RDD is rare, but when present, usually occurs in the extra-axial compartment². We present an unusual pattern of disseminated CNS RDD that involves both

extra- and intra-axial compartments of the brain and spine.

Case presentation

A 26-year-old woman presented to an outside institution with a two-year history of fatigue, joint aches, nausea/vomiting, blurry vision, polyuria, polydipsia and 120-pound weight gain. An ophthalmologic examination for blurry vision noted a left visual field deficit. Subsequent brain MRI showed an enhancing hypothalamic and suprasellar mass. A biopsy of this mass at the outside institution was not definitive, but was favored to represent an astrocytic neoplasm. The patient was transferred to

our institution for repeat biopsy. At the time of presentation, the patient was anemic (Hemoglobin 10.7 g/dL), hyperglycemic (Hemoglobin A1c 8.3%), and hypernatremic (Na 149 mmol/L). Repeat contrast-enhanced brain MRI (Figure 1, Figure 2) was obtained for stereotactic guidance and demonstrated an avidly enhancing mass centered in the region of the hypothalamus (Figure 1), extending to suprasellar cistern and involving the infundibulum. There are additional numerous scattered enhancing nodules throughout the ependymal and leptomeningeal spaces (Figure 2).

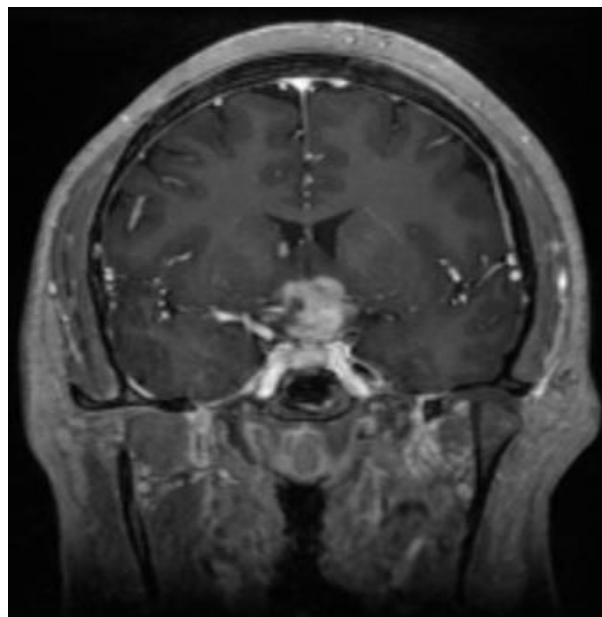


Figure 1. Coronal post-contrast T1-weighted MRI (repetition time msec/echo time msec, 7.2/2.7) of the brain centered at the level of the hypothalamus. An enhancing mass is present in the region of the hypothalamus (white arrowhead), with associated thickening of the of the pituitary infundibulum (white arrow).

Biopsy of the mass at our institution was consistent with RDD. Microscopic examination (Figure 3) demonstrated a nodular, dense population of enlarged histiocytes with ovoid, smooth nuclei, occasional macronucleoli, and abundant lightly eosinophilic granular cytoplasm, intermixed with scattered small lymphocytes in a background of neuropil (Figure 3A-D). Some cells appeared to contain internalized lymphocytes, suggestive of emperipolesis. Immunohistochemical studies

showed strong positivity for CD163 and CD68, thus establishing the histiocytic lineage; additional immunopositivity for S100 supported Rosai Dorfman disease rather than other histiocytic disorders such as Erdheim Chester disease. There were no reniform or grooved nuclei, and only rare cells showed CD1a immunoreactivity, confirming a non-Langerhans cell histiocytosis. UCSF500 Next Generation Sequencing demonstrated a solitary fusion between the SLC44A1 gene on chromosome 9q31 and the BRAF gene on chromosome 7q34, resulting in an in-frame fusion protein. The presence of a solitary pathogenic alteration affecting the BRAF oncogene and causing activation of the Ras-Raf-MAP kinase signaling pathway is consistent with a clonal histiocytic disorder and supports the morphologic and immunohistochemical diagnosis of Rosai-Dorfman disease.

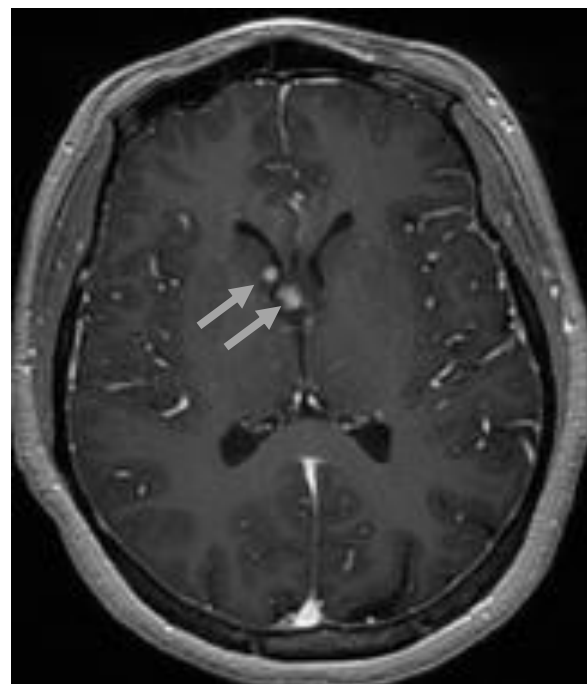


Figure 2. Axial post-contrast T1-weighted MRI (repetition time msec/echo time msec, 7.2/2.7) of the brain centered at the level of the lateral ventricles demonstrates two regions of leptomeningeal nodular enhancement near the caudate head and the right foramen of Monro (arrows).

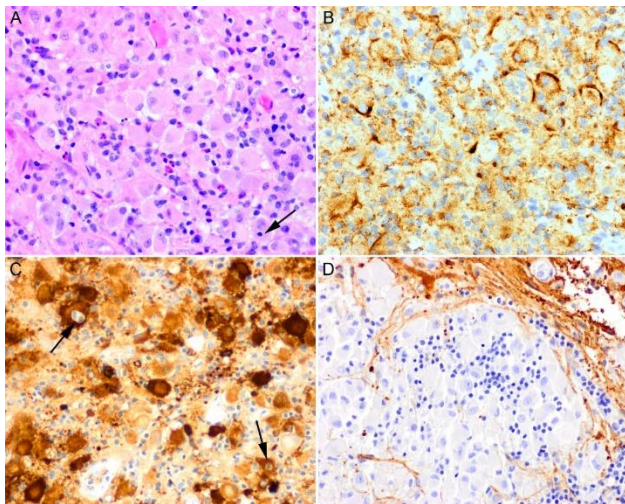


Figure 3. Histomorphology and immunochemical profile of Rosai-Dorfman disease involving the left hypothalamic lesion (400X magnification). H&E stain of the stereotactic biopsy material shows abundant histiocytes and lymphocytes (A). Histiocytes are strongly positive for CD68 (B) and S100 (C), an immunophenotype supportive of Rosai-Dorfman disease. Glial fibrillary acidic protein (GFAP) stain highlights background brain parenchyma and is negative in the histiocytes (D), providing no support for a glial neoplasm. Intact lymphocytes are seen within the cytoplasm of histiocytes, suggestive of emperipolesis (black arrows).

Subsequent to the diagnosis, MRI of the spine (Figure 4) and PET/CT (Figure 5) were performed for staging. Spine MRI demonstrated leptomeningeal and intramedullary spinal cord disease (Figure 4). F-18 FDG PET/CT revealed intense hypermetabolism related to the hypothalamic mass (Figure 5A), extending to involve the infundibulum, as well as hypermetabolic cervical, mediastinal and retroperitoneal lymphadenopathy (Figure 5B). The constellation of findings in this patient constitutes a rare case of RDD with craniospinal leptomeningeal dissemination and systemic lymphadenopathy.



Figure 4. Sagittal post-contrast T1-weighted MRI (repetition time msec/echo time msec, 589/16) of the cervical spine demonstrates multiple disseminated nodular foci of leptomeningeal enhancement (arrows).

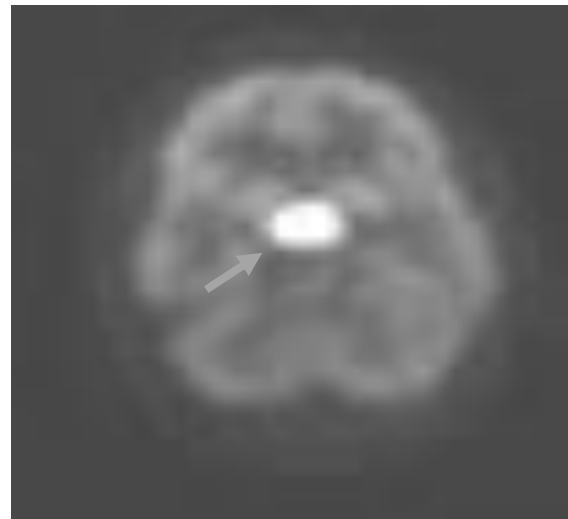


Figure 5(A): Axial reconstruction at the level of the hypothalamic mass of whole body F18-FDG PET/CT obtained 66 minutes after administration of 11.1 mCi of F18-FDG demonstrate avid hypermetabolism of the hypothalamic mass.



Figure 5(B): Anterior projection whole body rotating three-dimensional maximum intensity projection reconstruction of F18-FDG PET/CT obtained 66 minutes after administration of 11.1 mCi of F18-FDG. There is intense hypermetabolism associated with the hypothalamic mass and thickened infundibulum (white circle). There is also diffuse cervical (long arrow), mediastinal (small arrow) and retroperitoneal (dashed arrow) lymphadenopathy.

DISCUSSION

Rosai Dorfman disease, also known as sinus histiocytosis with massive lymphadenopathy, is a rare, histiocytic disorder that involves the overproduction of non-Langerhans histiocytes. These cells most often accumulate in the lymph nodes, but can also be seen in other areas of the body including the skin, sinonasal cavity, orbits, bones, salivary glands, and central nervous system. Autoimmune diseases and viral infections such as human herpesvirus 6 or Epstein-Barr virus have been postulated as potential inciting factors³. The typical manifestations of this disease include massive, painless cervical lymphadenopathy, weight loss and fever, usually in patients younger than 20 years of age.

The most common, though nonspecific, imaging feature of Rosai Dorfman disease is massive cervical lymphadenopathy¹. The majority of published cases are case reviews of atypical extra-nodal manifestations of disease. Intracranial disease is rare and can present either as dural-based masses⁴, often confused for meningiomas, or intraparenchymal masses, as in the case of our patient. Patients with intracranial disease tend to present later in life compared to patients with nodal disease, with a mean age at presentation of 34.9 years⁵. The most common locations for intracranial disease are dural, suprasellar, along the cerebral convexities, parasagittal, cavernous sinus, petroclival, and cerebellar⁵.

One third of patients with intracranial disease will also have extranodal manifestations elsewhere in the body. Systemic manifestations of Rosai Dorfman disease can affect the chest, abdomen, pelvis, breast, skeletal system and soft tissues. Thoracic manifestations commonly include mediastinal lymphadenopathy³ and less commonly, homogeneously enhancing masses^{6,7}. Cardiac manifestations occur in less than 1% of cases and usually appear as an enhancing intracardiac, pericardial or epicardial soft tissue mass.⁸ Abdominal manifestations commonly include retroperitoneal or mesenteric lymphadenopathy, but can occasionally include ill-defined, infiltrative soft tissue masses that mimic lymphoma. Soft tissue

involvement is seen in less than 10% of cases and can occur anywhere in the body.³ Osseous involvement, occurring in less than 10% of cases, usually manifests as lytic lesions in the metaphysis of long bones. Breast and reproductive organ involvement are exceedingly rare.

Previous published case reports of hypothalamic/suprasellar Rosai Dorfman disease have described similar imaging characteristics, also in patients with long-standing systemic symptoms of pituitary dysfunction.⁵ Several case reports of craniospinal disseminated Rosai Dorfman and intramedullary Rosai Dorfman also exist in the literature^{4,9,10}.

Brain and spine MRI as well as PET-CT are important in the staging of Rosai Dorfman disease, to evaluate for the extent of nodal and extra-nodal involvement. Additionally, follow-up imaging plays a key role in the evaluation of treatment response. Rosai Dorfman is a proliferative histiocytic disorder that requires treatment for symptomatic vital organ involvement. Complete spontaneous resolution of disease is seen in up to 20% of cases of systemic Rosai Dorfman disease, but there are no reported cases of spontaneous resolution of CNS disease¹⁰. For our patient with symptomatic pituitary dysfunction from her intracranial disease and systemic nodal involvement, high dose steroid therapy and chemotherapy were initiated. In patients with localized disease, however, surgical resection and radiotherapy are often utilized.

CONCLUSION

In summary, we present a rare case of systemic and disseminated craniospinal Rosai Dorfman disease with intraparenchymal and leptomeningeal involvement, but no sinus or dural-based involvement.

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