Head and Neck Pathology (2019) 13:656–660
https://doi.org/10.1007/s12105-018-0941-3

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Head and Neck Sinus Histiocytosis with Massive Lymphadenopathy Radiology–Pathology Correlation

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Received: 21 May 2018 / Accepted: 29 May 2018 / Published online: 31 May 2018

Abstract
Sinus histiocytosis with massive lymphadenopathy, or Rosai-Dorfman disease, is a rare, benign type of non-Langerhans cell histiocytosis. The radiological findings are often nonspecific, potentially mimicking malignancies. The diagnosis is ultimately made based on pathology, in which the lymph nodes are characterized by a dilated subcapsular sinus filled with histiocytes that can exhibit emperipolesis. Immunohistochemically, the histiocytes are variably CD68 positive and reliably negative for CD1a. The features of head and neck sinus histiocytosis with massive lymphadenopathy are exemplified in this radiology-pathology correlation sine qua non article.

Keywords Sinus histiocytosis with massive lymphadenopathy · Radiology · Pathology

History

The patient is an 8-year-old male with a history of asthma who presented with progressive non-painful right neck swelling for several weeks. Initially, the patient experienced a non-productive cough but no fevers, night sweats, weight loss, or fatigue. On physical examination, there was slightly limited range of motion of the neck due to bulky right cervical lymphadenopathy, but no overlying skin discoloration or tenderness. The lymph nodes were initially hard, but became larger and more rubbery at 3 months follow up. The white blood cell count was normal, but the ESR was elevated at 54 mm/hr. The infectious work-up was negative, including Bartonella titers.

Radiographic Features

Ultrasound of the neck demonstrated extensive bilateral lymphadenopathy, right more than left, in which the largest lymph node measured up to 3 cm (Fig. 1). The fatty hilum was preserved in most of the lymph nodes, which were not very hypervascular. CT of the neck with contrast was also performed at initial presentation and at 3 months, which showed generalized increase in size of the bilateral multilevel cervical lymphadenopathy with associated surrounding fat stranding (Fig. 2). Except for a single right neck lymph node with central hypoattenuation, the lymphadenopathy appeared to be solid. The differential diagnosis based on the imaging findings included infectious, inflammatory, and neoplastic conditions. ^{18}FDG-PET/CT performed at 3 months follow up showed corresponding hypermetabolism associated with the bilateral cervical lymphadenopathy, with a maximum of SUV of 8.9 (Fig. 3), but no evidence of disease beyond the neck.

Diagnosis

Biopsy of the lymphadenopathy was performed within 3 days of presentation at our institution and histological examination demonstrated effacement of the normal lymphoid architecture and a ‘mottled’ appearance, as well as rare reactive follicles with germinal centers, histiocytes in clusters and syncytia with abundant, pale, eosinophilic cytoplasm, and minimal atypia, and numerous plasma cells (Fig. 4). Some histiocytes demonstrated round contours with emperipolesis of mature lymphocytes and rare acute inflammatory cells. Both the histiocyte nuclei and cytoplasm

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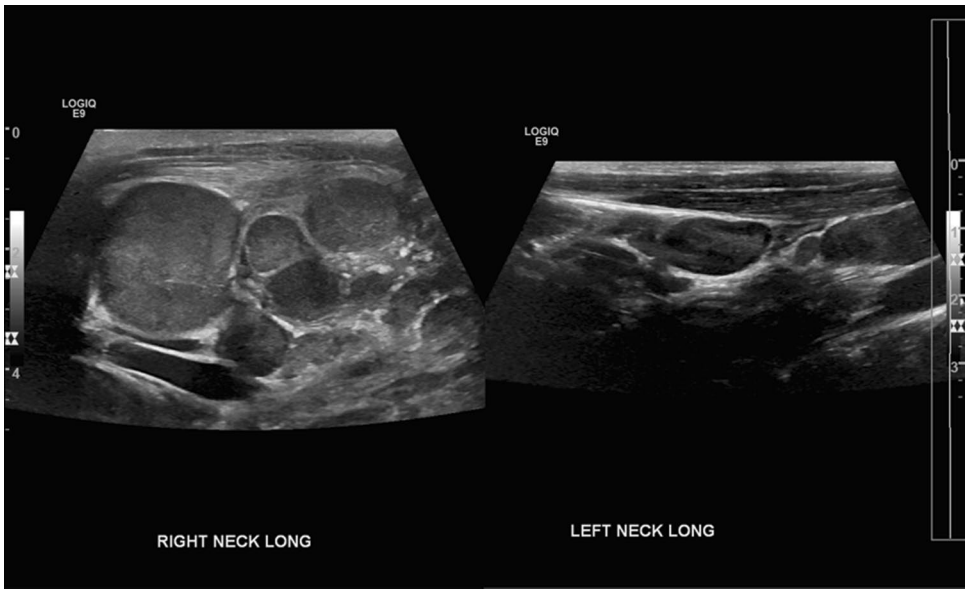

Fig. 1 Ultrasound image shows bilateral cervical lymphadenopathy, right more extensive than left

stained positive on S-100 immunohistochemistry, which highlighted the outer contours of the histiocytes and created a 'halo' effect around the mature cells engulfed by the histiocytes through emperipolesis. The cells were also CD1a negative. The findings were thus characteristic of intranodal sinus histiocytosis with massive lymphadenopathy.

Treatment

Clindamycin was administered to the patient at another institution emergency department initially based on the assumption that the patient had an infectious lymphadenitis. Otherwise, it was decided to observe the patient and obtain follow up imaging once the diagnosis of intranodal sinus histiocytosis with massive lymphadenopathy was made. Despite the increase in size of the lymphadenopathy on follow up at 3 months, no additional treatment was implemented since there was no compromise of vital structures and functions. At 6 months follow up, the lymphadenopathy spontaneously decreased in size.

Discussion

Sinus histiocytosis with massive lymphadenopathy, or Rosai-Dorfman disease, is a rare, benign type of non-Langerhans cell histiocytosis [1]. The pathogenesis of Rosai-Dorfman disease is not entirely clear, but RAF/MEK/ERK pathway mutations may be implicated, suggesting a clonal process at least in some cases [2]. The manifestations of Rosai-Dorfman disease may be attributable to monocyte recruitment with differentiation blockade and the production of various inflammatory molecules [3]. Rosai-Dorfman disease mainly affects children, adolescents, and young adults, with a slight male predominance [4]. Patients typically present with bulky bilateral painless cervical lymphadenopathy. However, there can also be extranodal sites of involvement, including within the skin, sinonasal cavity, salivary glands, and dura, for example [4–8]. Patients may experience fevers and have elevated inflammatory markers, such as ESR [4].

Various diagnostic imaging modalities are suitable for evaluating the lymphadenopathy in Rosai-Dorfman disease. Moreover, imaging can be useful for screening the extent of disease involvement and for follow-up. In particular, ^{18}FDG-PET/CT can help identify lesions that are not conspicuous on other modalities, although extranodal involvement can still be elusive [6–8]. However, the imaging features of the lymphadenopathy in Rosai-Dorfman disease are not specific. For example, the affected lymph nodes usually demonstrate homogenous enhancement on CT and MRI, which can resemble lymphoproliferative conditions, for example [5]. Furthermore, the ultrasound appearance and hypermetabolism on ^{18}FDG-PET of the affected lymph nodes can also mimic malignancies, such as lymphoma [8]. Nevertheless, Rosai-Dorfman disease should be considered in the differential diagnosis when there is massive painless bilateral cervical lymphadenopathy in young patients [8].

Ultimately, the diagnosis of Rosai-Dorfman disease is made based on histopathological examination. Microscopically, lymph node involvement is characterized by a dilated subcapsular sinus filled with histiocytes [4]. Due to the

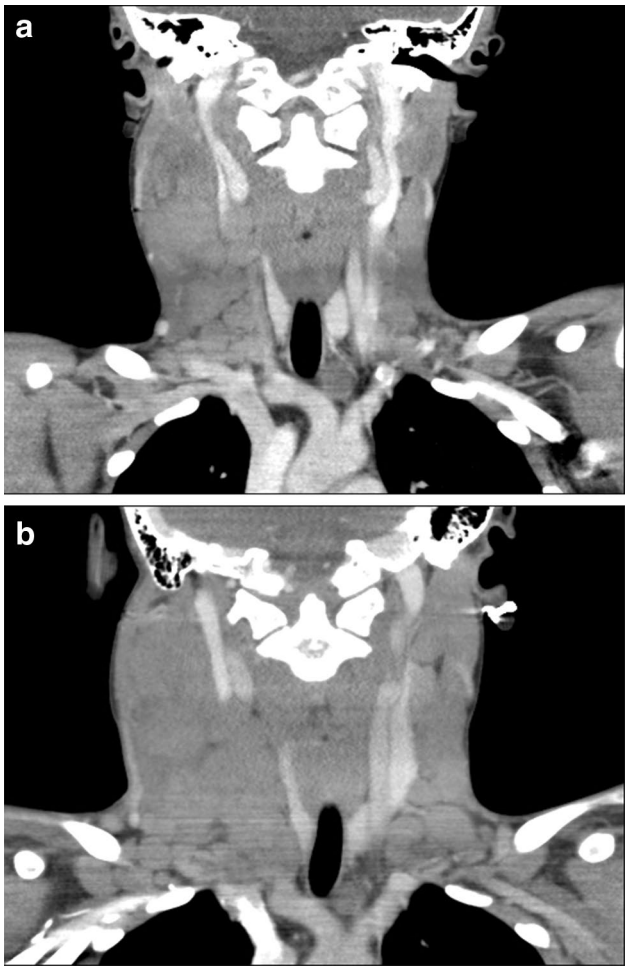

Fig. 2 Coronal post-contrast CT image at initial presentation **a** shows numerous multilevel enlarged and hyperenhancing cervical lymph nodes, right more extensive than left, with surrounding fat stranding. Coronal post-contrast CT image at 3 months follow up **b** shows generalized increase in size of the lymphadenopathy

proliferation of numerous histiocytes, a mottled appearance is often identified at low-power. Residual reactive lymphoid follicles with germinal centers may be seen. Fibrosis is also commonly identified [9]. Histiocytes in Rosai-Dorfman disease are characterized by abundant, eosinophilic cytoplasm

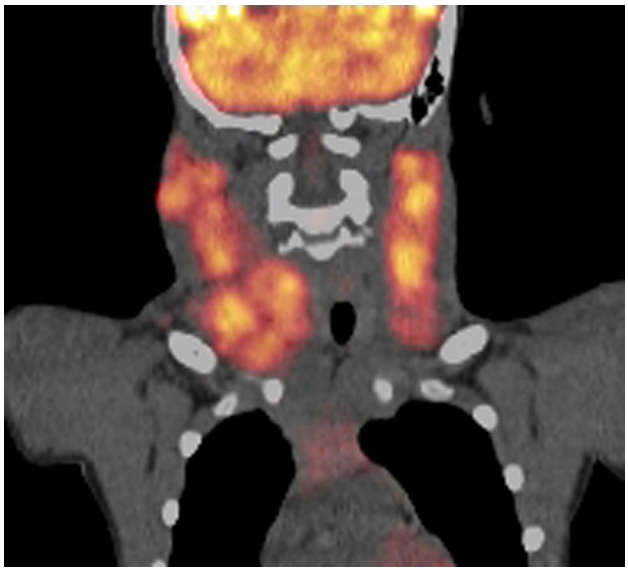

Fig. 3 Coronal fused ^{18}FDG-PET/CT image at 3 months follow up shows hypermetabolism associated with the bilateral cervical lymphadenopathy

with central, vesicular nuclei and small, but prominent nucleoli. The histiocytes can be arranged in nests, sheets, syncytia, or clusters and do not demonstrate atypia. Generally, pockets of polyclonal plasma cells are present between histiocyte populations [9, 10]. Granulocytes are generally not encountered in intranodal Rosai-Dorfman disease. Necrosis and mitosis are also rare [9].

Classically, histiocytes in intranodal Rosai-Dorfman disease engulf small lymphocytes, plasma cells, and erythrocytes without phagocytosis. This process, known as emperipolesis, can be identified on routine hematoxylin and eosin stains. Immunohistochemical staining for S100, which highlights the nuclei and cytoplasm of histiocytes, can make this process more conspicuous by demarcating histiocyte edges and creating a 'halo' effect around mature cells within the cytoplasm [9, 11]. Immunohistochemically, the histiocytes are variably CD68 positive and reliably negative for CD1a and Langerin [9,

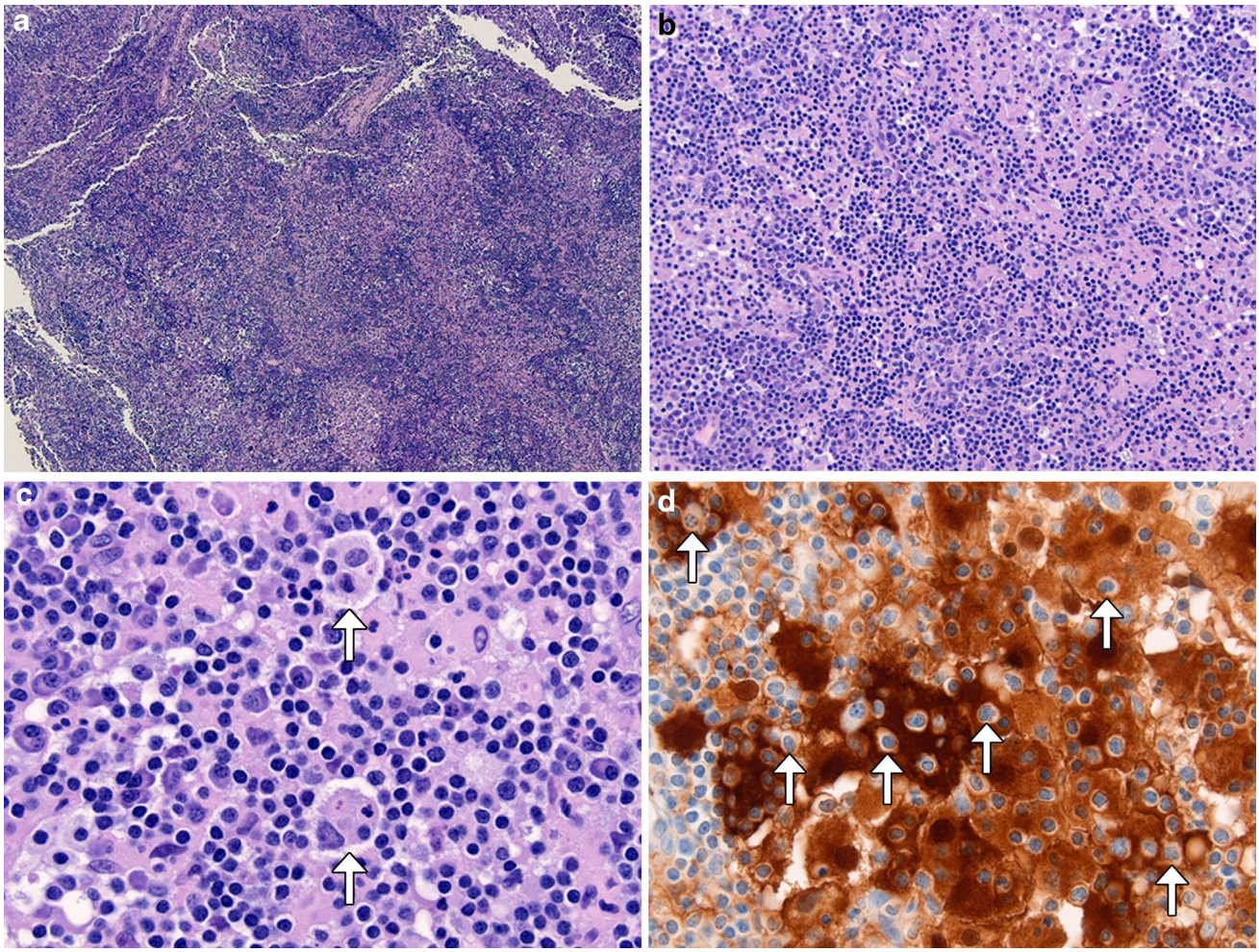

Fig. 4 Low-power (4X) hematoxylin and eosin stained photomicrograph demonstrates effacement of the normal lymphoid architecture and a 'mottled' appearance (**a**). Some rare reactive follicles with germinal centers are present. A mid-power (20X) hematoxylin and eosin stained photomicrograph demonstrates histiocytes in clusters and syncytia with abundant, pale, eosinophilic cytoplasm (**b**). Minimal atypia is present in the histiocytes. At high power (60X), numerous plasma cells are identifiable. Some histiocytes demonstrate round contours with emperipolesis (arrows) of mature lymphocytes and rare acute inflammatory cells (**c**). Immunohistochemical staining with S-100 further illustrates the process of emperipolesis (**d**). Both the histiocyte nuclei and cytoplasm are stained by S-100 immunohistochemistry, which serves to highlight the outer contours of the histiocytes and creates a 'halo' effect around the mature cells engulfed by the histiocytes through emperipolesis (arrows)

11]. The background lymphocytes and plasma cells, including those engulfed by the histiocytes, are polyclonal [10].

Since Rosai-Dorfman disease is often self-limited, clinical observation without treatment is pursued when possible [4, 6]. However, when there is compromise of vital organ or significant clinical symptoms, steroids and surgical debulking may be necessary. Otherwise, chemotherapy, radiation therapy, or immunomodulation can be considered in recalcitrant cases of Rosai-Dorfman disease [4, 6].

References

1. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a pseudolymphomatous benign disorder. Analysis of 34 cases. Cancer. 1972;30:1174–88.
2. Shanmugam V, Margolskee E, Kluk M, Giorgadze T, Orazi A. Rosai-Dorfman disease harboring an activating KRAS K117N missense mutation. Head Neck Pathol. 2016;10:394–9.
3. Cai Y, Shi Z, Bai Y. Review of Rosai-Dorfman disease: new insights into the pathogenesis of this rare disorder. Acta Haematol. 2017;138:14–23.
4. Dalia S, Sagatys E, Sokol L, Kubal T. Rosai-Dorfman disease: tumor biology, clinical features, pathology, and treatment. Cancer Control. 2014;21:322–7.

5. Xu Q, Fu L, Liu C. Multimodality imaging-based evaluation of Rosai-Dorfman disease in the head and neck: a retrospective observational study. Medicine. 2017;96:e9372.
6. Averitt AW, Heym K, Akers L, Castro-Silva F, Ray A. Sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman disease): diagnostic and treatment modalities for this rare entity revisited. J Pediatr Hematol Oncol. 2018;40:e198–202.
7. Raslan OA, Schellingerhout D, Fuller GN, Ketonen LM. Rosai-Dorfman disease in neuroradiology: imaging findings in a series of 10 patients. AJR Am J Roentgenol. 2011;196:W187–93.
8. La Barge DV 3rd, Salzman KL, Harnsberger HR, Ginsberg LE, Hamilton BE, Wiggins RH 3rd, Hudgins PA. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): imaging manifestations in the head and neck. AJR Am J Roentgenol. 2008;191:W299–306.
9. Kroft SH. Rosai-Dorfman disease: familiar yet enigmatic. Semin Diagn Pathol. 2016;33:244–53.
10. Paulli M, Bergamaschi G, Tonon L, Viglio A, Rosso R, Facchetti F, Geerts ML, Magrini U, Cazzola M. Evidence for a polyclonal nature of the cell infiltrate in sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). Br J Haematol. 1995;91:415–8.
11. Colmenero I, Molho-Pessach V, Torrelo A, Zlotogorski A, Requena L. Emperipolesis: an additional common histopathologic finding in H syndrome and Rosai-Dorfman disease. Am J Dermatopathol. 2012;34:315 – 20.