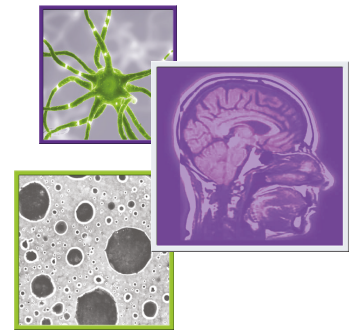
Case Report

CNS Oncology



Cerebral manifestation and diagnostic dilemma of Rosai-Dorfman disease

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Practice points

- Rosai-Dorfman disease (RDD) is a rare, S100-positive histiocytic proliferation, that can cause both nodal and extranodal illness.
- We present a case of a 53-year-old male patient. Magnetic resonance imaging described a plaque-like meningeal lesion, and the preoperative diagnosis was meningioma.
- Histologically, dense infiltration of lymphocytes, plasma cells, and histiocytes was seen, furthermore, the presence of emperipolesis in the sample was pronounced. In the histiocytes nuclear and cytoplasmic positivity with S100 protein, and nuclear positivity with Cyclin D1 was observed. The case was concluded as RDD.
- Morphological appearance of intracranial RDD with imaging procedures can present a differential diagnostic challenge. The correct diagnosis is based on the presence of histiocytes with emperipolesis, and properly defined immunohistochemical characteristics.

Rosai-Dorfman disease (RDD) is a rare, S100-positive histiocytic proliferation, that can cause both nodal and extranodal illness. We present a case of a 53-year-old male patient. Magnetic resonance imaging described a plaque-like meningeal lesion, and the preoperative diagnosis was meningioma. Histologically, dense infiltration of lymphocytes, plasma cells, and histiocytes was seen, furthermore, the presence of emperipolesis in the sample was pronounced. In the histiocytes nuclear and cytoplasmic positivity with S100 protein, and nuclear positivity with Cyclin D1 was observed. The case was concluded as RDD. Morphological appearance of intracranial RDD with imaging procedures can present a differential diagnostic challenge. The correct diagnosis is based on the presence of histiocytes with emperipolesis, and properly defined immunohistochemical characteristics.

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Rosai-Dorfman disease (RDD), otherwise formerly known as massive lymphadenopathy with sinus histiocytosis is a rare, S100-positive histiocytic proliferation, that can cause nodal and extranodal illness, as well [1,2]. The classic manifestation includes fever, leukocytosis, and bilateral cervical lymphadenopathy [3].

According to the current, 5th edition of the World Health Organization's (WHO) Classification of Haematolymphoid Tumours, the essential diagnostic criteria encompass the presence of enormous S100 positive histiocytes with abundant pale cytoplasm, round nucleus, and prominent nucleoli, while numerous plasma cells are visible in the background. Furthermore, Cyclin D1 and Oct-2 expression, CD1a, CD207, and *ALK* absence are desirable criteria [2].

Extranodal RDD cases mainly occur in the fifth decade of life, while nodal RDD cases appear in the second and third decades, although it has been described in all ages [2,4]. Even though RDD more often affects men over women in general, cutaneous RDD occurs in Asian women more often [5]. Relevant literature data about the proportion of familial and sporadic cases of RDD are not available.

The etiology of RDD is yet unknown, and the pathogenesis is barely understood. Specific mutations of familial RDD disease are not yet identified, but various uncommon inherited disorders, such as heterozygous germline mutations in *TNFRSF6* gene encoding Fas, leads to Fas deficiency, and disorders associated with germline mutations

in the nucleoside transporter SLC29A3 (Familial histiocytosis syndrome (H syndrome)), could predispose to familial RDD. In half of the cases, gain-of-function mutations affecting the MAPK/ERK pathway were identified, including *KRAS, NRAS, MAPK21, ARAF, CSF1R*, and in several cases *BRAF* V600E. The molecular pathologic examination should contain *SLC29A3*, and *TNFRSF6* germline mutation analysis in suspected familial RDD cases. In sporadic RDD cases, predisposing mutations have not yet been described [2,3].

RDD often resolves spontaneously in non-intracranial cases. Surgical intervention is needed, if the disease affects the upper airways, the spinal cord, or other organs are endangered, especially in intracranial RDD cases, that could result in uncertain neurological symptoms. If the disease is persistent or recurring, patients are given MEK inhibitors. Adverse prognosis is considered in those patients, who have immune dysregulation, or the disease affects the kidneys, the tracheobronchial tract, or the liver. In 5–11% of cases, disease-specific death has been described [2,4,6].

Histological manifestations of lymph nodes include dilated sinuses, filled with lymphocytes, plasmocytes, and histiocytes. The most characteristic feature is the presence of intact haemopoietic cells in the cytoplasm of the histiocytes, a feature known as emperipolesis. In cases of extranodal manifestation, fibrosis is a common finding as well, with completely or partially storiform appearance. Furthermore, a large number of Immunoglobulin G4 (IgG4) positive cells in the lymphoplasmacytic infiltration, and obliterative phlebitis could be present [7,8]. In most cases, RDD affects the lymph nodes, especially in the cervical region. In almost half of the cases, RDD shows extranodal manifestation, such as the skin, the head and neck region, and the central nervous system [2].

Extranodal RDD manifestations are between 25% to 40% of all the RDD cases [8]. According to our literature research in PubMed with key words cerebral, and Rosai-Dorfman disease, 196 articles could be currently found about the cerebral RDD. These articles include single case reports, multiple case reports, reviews and radiological, pathological findings in central nervous system manifestations.

Case presentation

Hereby we present a case of a 53-year-old male patient with a medical history of benign essential hypertension. His first symptoms included repeating episodes of epileptic seizures with weakness, stiffness, insensitivity, and twitching of his right lower extremity. He was admitted to the Neurosurgical Department for further examinations. Magnetic resonance imaging (MRI) described a plaque-like meningeal lesion above the medial part of the left postcentral region, with the maximum thickness of 1–1,5 cm, and the extension of 5–6 cm. Around the lesion, oedema was visible, but no signs of propagation were seen. The preoperative diagnosis was meningioma, based on the morphological appearance on the MRI. Craniotomy was performed with resection of the infiltrated dura mater. After the surgery, the patient was observed for 5 days. He was let home with moderate paresthesia in his right arm and leg. Further therapy was not applied.

Histological sample was taken from the left parietal lobe and the adjacent meninx. Histologically, extensive fibro-inflammatory process of the dura mater with dense infiltration of lymphocytes, plasma cells, and histiocytes was seen (Figure 1A). The fibrosis had storiform and perivascular "onion-skin" like pattern focally, alongside lymphoplasmacytic infiltration. Obliterative phlebitis was not present (Figure 1B). Histiocytes of large size and wide, foamy eosinophilic cytoplasm were identified. The presence of emperipolesis in the sample is pronounced (Figure 1C). GFAP immunohistochemistry (IHC) showed exclusive positivity of the brain parenchyma. In the histiocytes, granular cytoplasmic positivity with CD68 (Figure 1D), nuclear and cytoplasmic positivity with S100 protein (Figure 1E), and nuclear positivity with Cyclin D1 was observed (Figure 1F). The lymphoid cells consisted of properly distributed B- and T-cells, proven by CD20, CD4, and CD8 IHC reactions. The incorporated lymphocytes were negative with S100, and Cyclin D1, as well. The amount of IgG4 positive plasma cells was more than 50/10 HPF focally, with a rate about 50% of all plasma cells (Figure 1G, Figure 1H). The histological morphology and the results of the IHC was concluded as RDD.

The patient became symptomless 3 weeks after the surgery, and remains ever since (disease-free and overall survival: 14 months).

Discussion & conclusion

Morphological appearance of intracranial RDD with imaging procedures can present as a differential diagnostic challenge. The dural mass mimics tumorous lesions, like meningiomas, which present as much more common lesions of the meninges. Surgical resection and histological examination is necessary for the differential diagnosis. Without surgery, RDD resolves spontaneously in most of the cases.

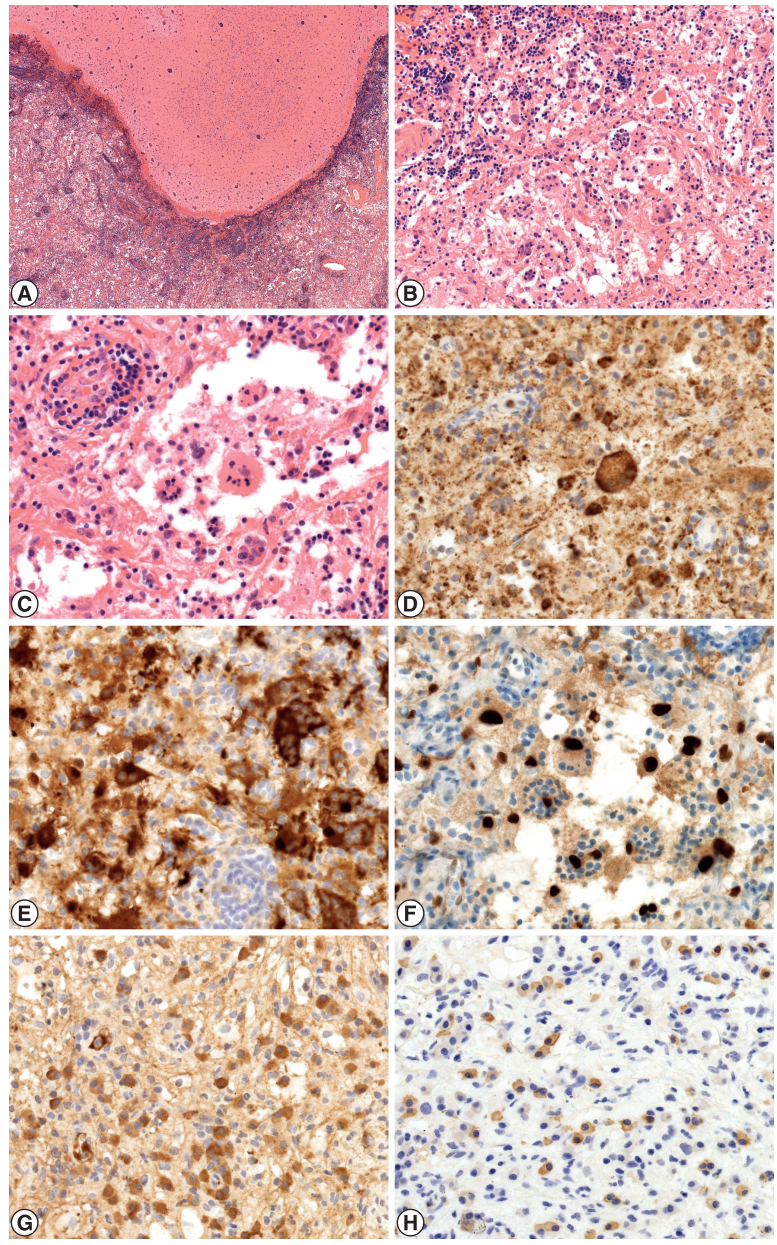

Figure 1. Morphological characteristics of Rosai-Dorfman disease (RDD). (A) Histologically, a cell-rich lesion with inflammatory stroma is visible, resulting in plaque-like thickening of the dura mater. The lesion is clearly separated from the normal brain tissue, and is not infiltrative. On low-magnification, the lesion mimics an inflammatory pseudotumor (hematoxylin and eosin [HE], 2.5x). **(B)** A mixture of vessels, collagen fibres, lymphocytes, and plasma cells are present, in specific, perivascular orientation, alongside with large histiocytes located in tissue gaps. The histiocytes have abundant, clear cytoplasm, with incorporated lymphocytes. The phenomenon is called emperipolesis, a characteristic feature of RDD (HE, 20x). **(C)** Histologic features of emperipolesis. Frequently, the histiocytes have vesicular chromatin pattern, and dot-like nucleoli. The vessels are surrounded by lymphocytic mantles (HE, 40x). **(D)** With cluster of differentiation 68 (CD68) immunohistochemistry (IHC) reaction, intensive, granular cytoplasmic positivity is seen in the histiocytes (CD68, 40x). **(E)** RDD histiocytes show aberrant S100 protein positivity. The ingested lymphocytes remain negative with this marker (S100, 40x). **(F)** A particular feature of RDD is the histiocyte nuclear positivity with cyclin D1 IHC. The ingested lymphocytes are negative (cyclin D1, 40x). **(G)** The plasma cells reflect Immunoglobulin G (IgG) positivity (IgG, 40x). **(H)** The majority of plasma cells are IgG4 positive (IgG4, 40x).

RDD remains both a peculiar disease and a challenging diagnosis. Recently, clonal genetic differences were identified that confirm the neoplastic nature of RDD. On low-magnification, the inflammatory pseudotumor-like picture, and the IgG4 positive plasma cells always have to raise suspicion for IgG4 disease.

The main differential diagnostic dilemmas include sinus histiocytosis and Erdheim-Chester disease. In sinus histiocytosis, the macrophages' size is characteristically smaller, compared with RDD, furthermore, the histiocytes are S100 negative, and there is no sign of emperipolesis. Erdheim-Chester disease does not possess the typical lymphoplasmacytic background, and the histiocytes are S100 negative, as well, and emperipolesis is not present either.

The correct diagnosis of RDD is based on the presence of histiocytes with emperipolesis, and properly defined IHC characteristics, such as aberrant S100 positivity in histiocytes, in spite of that ingested lymphocytes remain negative with S100 IHC.

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Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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