A 63 YEAR OLD WOMAN WITH WHITE MATTER LESIONS AND PACHYMENINGEAL INFLAMMATION

Ari Breiner, MD¹; William Dubinski, MD²; Bruce Gray, MD³; David G. Munoz, MD, FRCPC²

¹ Neurological Institute of New York, Columbia University Medical Center—New York, New York, USA.

² Division of Pathology, St. Michael's Hospital, University of Toronto-Toronto, Ontario, Canada.

³ Division of Diagnostic Imaging, St. Michael's Hospital, University of Toronto-Toronto, Ontario, Canada.

CLINICAL HISTORY

A 63-year-old woman, with a history of polycythemia vera, chronic splenomegaly, and osteoporosis, was admitted to our institution for investigation of progressive neurological and gastrointestinal symptoms. Eleven months prior, she noted pitting edema of the lower extremities, chronic watery diarrhea, and hypoalbuminemia. She underwent extensive gastrointestinal investigations, which revealed only hepatosplenomegaly. Ten months prior, she noted progressive neurological symptoms, including gait ataxia, generalized weakness, and episodic rotational vertigo. Brain MRI revealed multiple non-enhancing T2-hyperintense lesions in the periventricular white matter. Five months prior to admission to our hospital, she suffered a right thalamic lacunar stroke, causing left hemibody numbness. CT angiography demonstrated a dissection of the right vertebral artery.

On admission to our hospital, the patient complained of severe abdominal tenderness, with peritoneal signs, and underwent urgent laparotomy. There were no abnormal intraoperative findings, and biopsies taken from the stomach, duodenum, and rectum were normal. Gastroscopy and colonoscopy were performed, and were unrevealing. Post-operatively, the patient was encephalopathic, and minimally responsive. MRI of the brain again demonstrated abundant T2/FLAIR hyperintense (non-enhancing) lesions in the periventricular white matter and corpus callosum (Fig 1A: axial FLAIR sequence), consistent with central nervous system (CNS) demyelination. A small focus of enhancing T2/FLAIR signal hyperintensity in the right thalamus was suggestive of chronic thalamic stroke. The dura was diffusely thickened, and uniformly enhancing, following administration of gadolinium (Fig 1B; axial T1 gadolinium sequence). The differential diagnosis of this new dural process included infectious, malignant, and autoimmune causes. Clinically, the patient continued to deteriorate, and expired three days later.

GROSS AND MICROSCOPIC PATHOLOGY

Open dural biopsy was performed prior to the patient's death, and revealed a polymorphic inflammatory cell infiltrate, consisting principally of sheets of large, epithelioid histiocytes with foamy cytoplasm. Many histiocytes contained intact lymphocytes or plasma cells within their cytoplasm, a phenomenon known as emperipolesis (Fig 2; scale bar = $100 \,\mu$ m; inset, scale bar = $25 \,\mu$ m).

At autopsy, gross examination of the brain revealed a discoloured and thickened dura. Microscopically, the entire dura mater was infiltrated by foamy histiocytic cells demonstrating *emperipolesis*, as described above. The right vertebral artery was focally thickened, with aneurysmal dissection at the site (Fig 3). Microscopically, the artery (Fig 4; scale bar = $500 \,\mu\text{m}$; inset scale bar = $25 \,\mu\text{m}$) showed vessel wall infiltration and destruction by inflammatory cells. There was a 3 mm infarct in the right thalamus.

Coronal gross sections of the cerebral hemispheres revealed multiple, small (0.1–1.4 cm), sharply demarcated lesions in the subcortical white matter (Fig 5a). Microscopic brain examination revealed that these subcortical lesions were due to a second, *distinct* pathological process, consisting of plaques of demyelination, located in the subcortical white matter, corpus callosum, periventricular regions, and multiple brainstem segments (Fig 5b; Luxol fast blue stain; scale bar = 1000 μ m). These plaques demonstrated complete demyelination, with preservation of axons (Fig 5c; neurofilament stain; scale bar = 1000 μ m), and an absence of active inflammation. Samples obtained at the time of autopsy demonstrated mutation in the JAK2 tyrosine kinase, confirming a diagnosis of polycythemia vera". What are the two diagnoses?

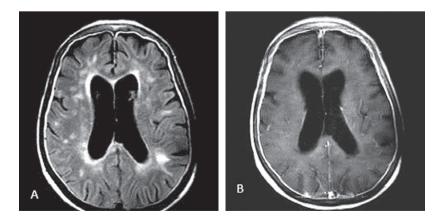


Figure 1.

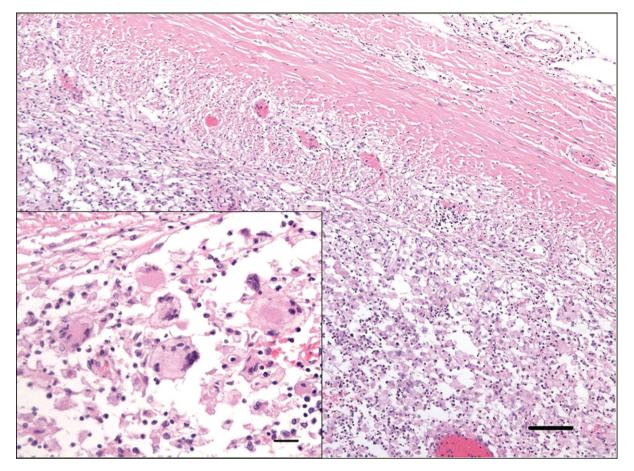


Figure 2.

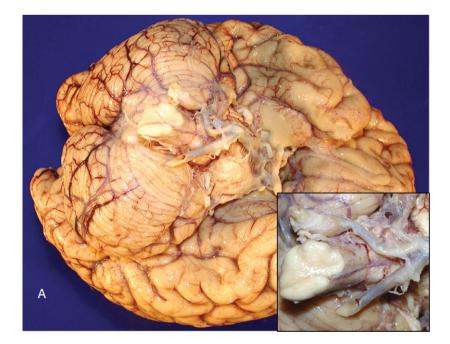


Figure 3.

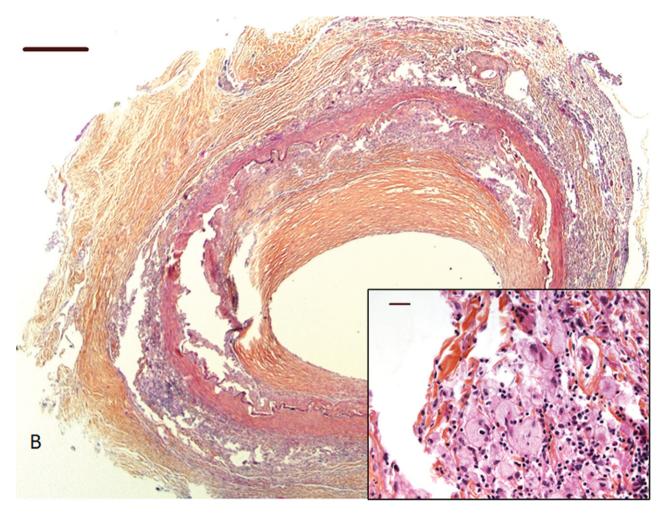


Figure 4.

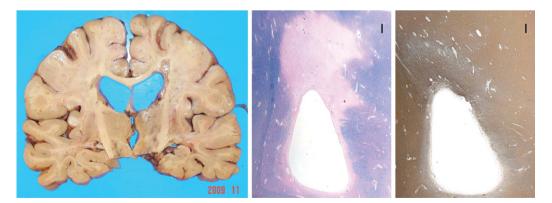


Figure 5a, b and c.

DIAGNOSES

1. CNS Rosai Dorfman disease.

2. Multiple sclerosis.

DISCUSSION

Rosai-Dorfman disease (sinus histiocytosis with massive cervical lymphadenopathy) was first described in 1969 (6); it is an immune disorder characterised by proliferation of B and T lymphocytes, and foamy histiocytes. The pathologic hallmark is emperipolesis, wherein histiocytes engulf lymphocytes and plasma cells within their cytoplasm. Rosai-Dorfman disease is typically confined to the lymph nodes, and the largest case series to date (423 cases) reports central nervous system (CNS) involvement in only 4% (2). A review of the CNS manifestations of Rosai-Dorfman disease reveals that the vast majority of patients present with focal duralbased hemispheric brain lesions mimicking meningioma (3), (1). Other reported sites of CNS involvement have included anterior optic pathway, cerebellopontine angle, spinal cord, or hemispheric white matter (3), (1). The present case expands the neurologic manifestations of Rosai-Dorfman disease to include intracranial arterial dissection (due to infiltration by inflammatory cells); and lends support to a prior report of diffuse dural inflammation in CNS Rosai-Dorfman disease, mimicking idiopathic hypertrophic pachymeningitis (7).

Multiple sclerosis (MS) is a chronic demyelinating neurological disorder, with a presumed autoimmune mechanism. The classical neuropathological findings in a chronic inactive MS plaque include a region of oligodendrocyte (myelin) loss, with relative preservation of axons, and minimal active inflammation or myelin breakdown products (4). These classical pathological findings were all observed in our patient.

Our case was quite atypical due to the co-existence of MS, Rosai-Dorfman disease, and polycythemia vera (all rare diseases) in a single patient. While the overlap may have been coincidental, one could raise the question of a common pathogenic mechanism, due to an underlying dysimmune state. In fact, some links between polycythemia vera and multiple sclerosis have already been established. Polycythemia vera is commonly caused by a somatic V617F mutation of the JAK2 tyrosine kinase, which is involved in signal transduction in both hematopoietic cells, and in cytokine receptors. IL-12 signalling through the JAK-STAT pathway plays a critical role in the pathogenesis of experimental autoimmune encephalitis (EAE), a Th1 cellmediated disease model of multiple sclerosis (5). One could speculate whether JAK2 mutations may provide a link in the understanding of multiple sclerosis, Rosai-Dorfman disease, and polycythemia vera.

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ABSTRACT

We describe the case of a 63-year-old woman with CNS Rosai-Dorfman disease, presenting with diffuse dural infiltration, mimicking idiopathic hypertrophic pachymeningitis, and right vertebral artery dissection. Her symptoms included a progressive 11-month history of vertigo, gait ataxia, and right thalamic stroke. A diagnosis of CNS Rosai-Dorfman disease was made following open dural biopsy, and later confirmed on autopsy studies. The autopsy demonstrated widespread dural infiltration by inflammatory cells, principally large histiocytes, many of which exhibited *emperipolesis*, a characteristic finding in Rosai-Dorfman disease. A second pathological finding on autopsy was the presence of multiple demyelinating plaques (with preservation of axons), located in the corpus callosum, periventricular white matter, and multiple brainstem segments. These were consistent with a diagnosis of multiple sclerosis.

This case description serves to remind clinicians that CNS Rosai-Dorfman disease—although uncommon—may present as a focal, dural-based, hemispheric mass lesion, or as diffuse pachymeningeal inflammation. Our case was also unusual due to the co-existence of CNS Rosai-Dorfman disease, multiple sclerosis, and polycythemia vera (all rare diseases) in a single patient. Although the overlap of disorders may have been co-incidental, one could raise the question whether all three disorders were triggered by the same underlying dysimmune state.