Successful treatment with azathioprine of relapsing Rosai-Dorfman disease of the central nervous system

Case report

GUILLAUME LE GUENNO, M.D.,1 LIONEL GALICIER, M.D.,2 EMMANUELLE URO-COSTE, M.D., PH.D.,3 VIRGINIE PETITCOLIN, M.D.,4 VIRGINIE RIEU, M.D.,1 AND MARC RUIVARD, M.D., PH.D.1

Departments of 1Internal Medicine and 2Radiology, Hôpital Estaing, Clermont-Ferrand; 2Department of Clinical Immunology, Hôpital Saint Louis, Assistance Publique–Hôpitaux de Paris; and 3Department of Pathology, Hôpital du Rangueil, Toulouse, France

Rosai-Dorfman disease (RDD) is a rare non-Langerhans histiocytosis that usually presents with lymphadenopathy. Although isolated involvement of the CNS was considered to be uncommon, numerous cases have been reported in recent years. For RDD of the CNS, the treatment consists, in general, of surgery. In cases of partial resection or relapse, chemotherapy regimens, corticosteroids, and/or radiotherapy have yielded negative results. The authors describe the case of a 57-year-old man with a history of chronic Q fever who presented with aphasia and partial seizure. Computed tomography of the brain revealed a left frontotemporal lesion that was suggestive of a meningioma. The lesion was partially resected and histopathological evaluation revealed the presence of RDD. Nineteen months later, a Jacksonian seizure prompted MRI evaluation, which disclosed a local recurrence of the tumor. Computed tomography and FDG-PET demonstrated that the RDD involved no other site, but the presence of ileitis, noted on ileoscopy, led to the diagnosis of Crohn disease. Treatment with the purine analog azathioprine was initiated, leading to an objective and sustained response in both the RDD tumor and ileitis over 35 months of follow-up. This case report highlights the potential use of a purine analog in cases of relapsing RDD of the CNS and a possible common defect of macrophage regulation in RDD, Crohn disease, and Q fever.

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**Key Words** • Rosai-Dorfman disease • sinus histiocytosis • oncology • meningioma • azathioprine • Crohn disease

ROSAI-Dorfman disease, or sinus histiocytosis with massive lymphadenopathy, is a rare non-Langerhans histiocytosis of unknown etiology that usually presents with painless bilateral cervical lymphadenopathy. Extranodal involvement is common and is seen in approximately 40% of patients. Although isolated involvement of the CNS has been considered to be uncommon, numerous cases have been reported in recent years. The optimal strategy for the management of RDD has not yet been identified. In general, chemotherapies and radiotherapy show low efficacy. Testing for interferon-α was effective in 4 of 5 patients reported. For RDD of the CNS, the treatment consists in general of surgery, corticosteroids, and/or radiotherapy.

We describe an original case involving a male patient with an RDD meningioma-like intracranial lesion that occurred concurrently with Crohn disease. The patient suffered a relapse after partial resection, but showed an objective and prolonged response to the purine analog azathioprine.

**Case Report**

**History and Presentation.** This 57-year-old man had had relapsing febrile pericarditis since 1996. Chronic Q fever without endocarditis was diagnosed in 1997 (Phase I antibody IgG titer 1:1600; Phase II antibody IgG titer 1:3200) and was treated with doxycycline (200 mg daily) and hydroxychloroquine (400 mg daily). Despite this treatment, 3 episodes of dry pericarditis occurred in 2003, 2008, and 2009.

In May 2007, the patient presented with a report of

Abbreviation used in this paper: RDD = Rosai-Dorfman disease.
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a partial seizure with tremor of the right arm and Broca aphasia. Computed tomography of the brain (Fig. 1A) showed a left frontotemporal dura-based tumor. The mass was homogeneous and lobulated, with marked contrast enhancement. Angiography (Fig. 1B) via the external carotid artery revealed the lesion to be hypervascular and showed that it derived its blood supply from the meningeal arteries. However, the lesion appeared avascular when angiography was performed via the internal carotid artery (Fig. 1C). These findings were highly consistent with a meningioma.

An open biopsy was performed. The membranous mass was adherent to both the dura and the pia and was vascularized by the sylvian artery. Histopathological and immunohistochemical evaluation (Fig. 2) revealed a mixed cell population that was composed predominantly of mature histiocytes with evidence of emperipolesis without “doughnut granuloma.” The histiocytic cells showed positive reactions to antibodies against S100 and CD68 but no reaction to antibodies against CD1a. The results of polymerase chain reaction (PCR) testing for Coxiella in the CSF were negative. Treatment with levetiracetam was initiated.

In October 2008, a new Bravais-Jacksonian seizure led to an increase in the dose of levetiracetam. An MRI study performed in December 2008 (Fig. 3A) revealed a relapse of the frontotemporal condition, with a tissue lesion that showed an isointense signal on both T1- and T2-weighted sequences and enhanced after injection of gadolinium. A thoracic and abdominal CT scan revealed terminal ileitis without lesions, which was suggestive of RDD. The patient was referred to our unit in January 2009.

**Examination.** Clinical examination showed sensitivity of the right iliac fossa with intermittent bloody diarrhea following abdominal pain, which was suggestive of Koenig syndrome. The neurological evaluation revealed a minor positional tremor of the right arm. Blood tests showed an elevated number of white blood cells with neutrophilia (8.47 × 10⁹ cells/L), monocytes (1.95 × 10⁹ cells/L), anemia (10.8 g hemoglobin/dl), and an increased level of C-reactive protein (44 mg/L). Protein plasma electrophoresis showed a normal level of albumin with increased γ-globulin (20.6 g/L). The results of immunological tests (antinuclear antibodies, rheumatoid factor, antiglobulin test) were negative, expect that antibodies against *Saccharomyces cerevisiae* were present at 20 U/ml (< 16). The results of liver function tests and the serum lactate dehydrogenase level were normal. Blood flow cytometry did not reveal any abnormal population. The Q fever serology revealed a cicatricial profile (Phase I antibody IgG titer 1:50). Treatment with hydroxychloroquine and doxycycline was stopped. An FDG-PET study demonstrated isolated fixation in the ileum. Endoscopy of the gastrointestinal tract revealed numerous superficial ulcerations of the ileum with cryptic abscesses but without granulomas, which was consistent with Crohn ileitis. Magnetic resonance imaging of the brain revealed a stable frontotemporal tumor.

**Treatment and Follow-Up.** Treatment with azathioprine (150 mg daily) combined with oral budesonide (9 mg daily) was begun in February 2009. The digestive symptoms and the inflammatory syndrome improved 1 week later. The dose of azathioprine was decreased to 100 mg daily because of a low platelet count (51 × 10⁹/L); budesonide treatment was stopped after 3 months. In May 2009, the tumor was stable on MRI, and in September 2009, there was a slight decrease in size (Fig. 3B). In March 2010, the patient was hospitalized for treatment of multiple temporal lobe seizures with paresthesia of the...
right lips and arm and auditory hallucinations. A lumbar puncture revealed no abnormality, and CT of the brain showed a marked decrease in the size of the tumor; electroencephalography confirmed temporal lobe epilepsy. An MRI study performed 1 month later showed complete regression of the tumor (Fig. 3C). The antiepileptic treatment was increased with the addition of oxcarbazepine and clobazam.

In January 2012, after 35 months of azathioprine therapy, MRI showed a sustained and complete response (Fig. 3D).

Discussion

This case report described a typical case of isolated intracranial RDD. However, 2 unusual features should be noted: 1) its occurrence in the context of 2 other diseases that involve the monocyte/macrophage system, namely, Q fever and Crohn disease; and 2) it is, to our knowledge, the first case in which the efficiency of azathioprine treatment in RDD has been documented.

As in this patient, isolated RDD of the CNS usually occurs in middle-aged men without general symptoms. Intracranial RDD presents typically as a meningioma-like, extraparenchymal, dura-based mass in the convexity or base of the skull. On MRI, the lesions are similar to meningioma, with homogeneous, lobulated, and isointense lesions in the brain parenchyma that show strong homogeneous enhancement after injection of gadolinium on T1-weighted images. On T2-weighted images, the lesions appear heterogeneously hypo- to isointense, with an intensity that is similar to that of the adjacent dura matter. On angiography, lesions of RDD are typically hypovascular when compared with meningioma. Obviously this finding is not consistent, as shown by our case.

The optimum strategy for the management of RDD has not yet been identified. In cases of primary CNS RDD, radical resection is the ideal surgical goal. However, as in our case, the mass often adheres tightly to the cerebral cortex and may invade or surround other critical structures. As a consequence, many lesions are not completely resectable. Adjunctive irradiation has been used in some patients with variable efficiency. In general, chemotherapy regimens have yielded negative results; however, 2 children showed a sustained response to a combination of methotrexate and mercaptopurine. A high dose of interferon-α-2a, in particular the pegylated (polyethylene glycol–conjugated) form, has shown dramatic efficacy in cases of systemic RDD. However, we preferred to use azathioprine rather than pegylated interferon for several reasons: 1) Azathioprine is an efficient treatment for Crohn disease. It has the same mechanism of action as mercaptopurine, which has shown efficiency in RDD. 3) Interferon-α should be avoided in active Crohn disease and could favor the occurrence of seizures. The effect of azathioprine in this case of CNS RDD was apparent slightly after 7 months but was dramatic after 14 months.

Nevertheless, the potential relationship between a history of Q fever and the occurrence of RDD and Crohn ileitis remains unclear. No association of these 3 diseases is reported in the literature, with the exception of 1 case of RDD of the forearm that occurred during an episode of Crohn disease. On the other hand, the main type of cell that is implicated in the pathology of these 3 diseases is the monocyte/macrophage, which seems to be “immunodeficient.” Indeed, in chronic Q fever, monocytes have been shown to be defective in macrophage activity, with an atypical M2 activation program that promotes the Th2 response and the survival of Coxiella. In Crohn disease, macrophages show substantially impaired release of pro-inflammatory cytokines and a reduced ability to eliminate bacteria. In RDD, a “suppressor” phenotypic pattern for macrophages is suggested by the absence of Class II major histocompatibility complex (MHC) expression and the secretion of anti-inflammatory cytokines, such as interleukin-10 and transforming growth factor–β. These previously published data suggest that the occurrence of these 3 rare diseases in our patient was not coincidental.

In summary, our case report describes the use of a purine analog in a case of RDD, and a possible common defect in macrophage regulation in RDD, Crohn disease, and Q fever.

Disclosure

The authors have no conflicts of interest to declare in connection with this article.

Author contributions to the study and manuscript preparation

Fig. 3. Gadolinium-enhanced axial T1-weighted MR images of the brain. A: Image obtained in December 2008 showing frontotemporal recurrence. B: Image obtained after 7 months of azathioprine therapy showing a slight decrease in the size of the tumor. C and D: Images obtained after 14 (C) and 28 (D) months of azathioprine treatment showing complete regression of the lesion.
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Address correspondence to: Guillaume Le Guenno, M.D., Department of Internal Medicine, Hôpital Estaing, CHU, 1 Place Lucie Aubrac, 63000 Clermont-Ferrand, France. email: gleguenno@chu-clermontferrand.fr.