Neurosarcoidosis during the treatment of primary Sjögren's syndrome: is it a paradoxical effect of rituximab?

Sirs,

We report a 50-year-old Caucasian woman with past medical history of a well-characterised primary Sjögren's syndrome (pSS), who later developed neurosarcoidosis (NS) during the treatment with rituximab (RTX). Diagnosis of pSS was based on ocular/oral sicca symptoms, recurrent parotitis, non-erosive polyarthritis, and purpura on lower limbs. The patient tested positive for antinuclear antibodies, anti-Ro/SSA, anti-La/SSB, and rheumatoid factor. Tests for HIV, hepatitis B/C, anti-Sm, anti-dsDNA, and anti-CCP were negative. She had positive Schirmer's test, abnormal ocular staining score, and a labial salivary gland biopsy (LSGB) showing focal lymphocytic sialadenitis (focus score=4). As initial treatment, prednisone (10mg/day, with subsequent tapering) and low-dose methotrexate were started.

Two years later, she presented with a 3-month history of non-productive cough and dyspnea. Pulmonary function testing revealed reduced lung volumes (restrictive pattern). High-resolution computed tomography findings were suggestive of lymphoid interstitial pneumonia (LIP): ground-glass attenuation and thin-walled cysts, predominantly in the lower lobes. There was no pleural involvement or hilar/mediastinal lymphadenopathy. Bronchoalveolar lavage and lung biopsy were not performed due to the well-defined diagnosis of pSS, radiological findings suggestive of pSS-associated LIP, low-grade immunosuppression (only 10 mg methotrexate/week), and lack of relevant environmental exposure. During the following years, azathioprine and mycophenolate mofetil were used, but they had to be discontinued due to gastrointestinal intolerance. Monthly intravenous cyclophosphamide was the best tolerated treatment. However, after one year of cyclophosphamide with partial respiratory improvement, we opted for replacing this immunosuppressant by RTX (2x1g, two weeks apart) every 6 months.

Four months after the first RTX cycle, our patient reported persistent headache and reduced visual acuity. On that occasion, brain MRI found a solid expansive lesion in the hypothalamus, presenting intimate contact with the optic chiasm bifurcation (Fig. 1A-B). Other smaller lesions were observed in the cerebellum and in the left lateral ventricle.

Then, a cerebellar biopsy revealed a chronic inflammatory process with non-caseating epithelioid granulomas, compatible with sarcoidosis. The patient experienced remarkable neurological improvement with high-dose prednisone but became corticodependent. Even though anti-TNF agents are not effective for pSS (1), we indicated adalimumab here as an exception approach to treat NS considering: neurological severity, history of gastrointestinal intolerance to several oral immunosuppressants, and stability of the lung disease at that time. Under anti-TNF treatment, it was possible to completely wean off prednisone, while maintaining remission of the NS.

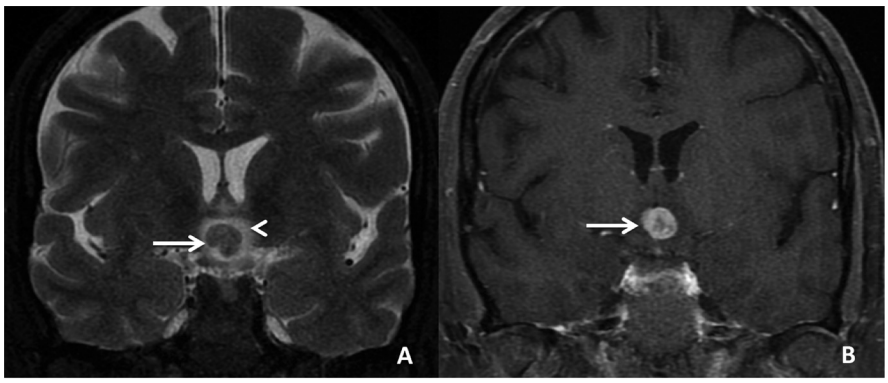

Fig. 1. Coronal T2 (1A) and post contrast T1 (1B) images. Solid expansive lesion (diameter of 1.2 cm) in the hypothalamus, with lobulated margins, showing predominantly T2 hypointensity (arrow in 1A) and heterogeneous post contrast enhancement (arrow in 1B). There is mild oedema in the surrounding parenchyma, characterised by T2 hyperintensity (arrowhead in 1A).

Although the occurrence of NS here may be fortuitous, it is difficult to ignore the temporal relationship between the RTX infusions and the onset of neurological symptoms. Notably, we found a few reported cases of possible RTX-induced sarcoidosis during the treatment of autoimmune diseases (2-4). Sarcoidosis is known to be a predominantly T-cell-mediated condition, but some evidence suggests B-cell dysregulation as contributor to its pathogenesis (5). Interestingly, rituximab has been reported as an alternative for treating refractory sarcoidosis, including NS (6). Regarding possible paradoxical effect while managing autoimmune diseases, we hypothesise that a RTX-induced imbalance in humoral/cellular immunity may rarely lead to the production of cytokines responsible for the sarcoid granuloma formation (3, 4, 7).

This case may raise another question: did our pSS patient have interstitial lung disease (ILD) as a manifestation of sarcoidosis before the treatment with RTX? We consider this possibility unlikely for two reasons. The first is the absence of hilar/mediastinal lymphadenopathy, as well as the absence of predilection for central regions and upper lobes, which are the most typical features of pulmonary sarcoidosis (8, 9). The second is the setting of a well-defined pSS with positive anti-Ro/SSA and a high focus score on LSGB, which have been shown to be risk factors for the development of pSS-ILD (10).

In summary, our case strengthens previous observations regarding a possible paradoxical effect of RTX when treating autoimmune diseases.

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