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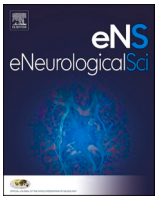

Letter to the Editor

Remission of idiopathic retroperitoneal fibrosis by ofatumumab as a disease-modifying therapy for multiple sclerosis

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Dear Editor,

It is not uncommon for multiple sclerosis (MS) patients to present with comorbid autoimmune disorders. However, there is no consensus therapy for this challenging situation. Nonetheless, if MS therapy can be repurposed for coexisting autoimmune diseases, the benefit is promising. In addition, because recruiting sufficient numbers of these complicated patients for large-scale clinical trials is difficult, the accumulation of case reports is more important [1]. Here, we show the first case of MS with retroperitoneal fibrosis that could be simultaneously treated by ofatumumab.

1. Case presentation

A 42-year-old male with an 8-year history of MS, severe obesity (body mass index >35), and emotional disturbance complained of back pain. He had met the criteria of McDonald diagnostic criteria of 2017, including cerebrospinal fluid oligoclonal bands [2]. After the 7.5-years use of interferon beta 1b, he used dimethyl fumarate for 6 months. Although there were no neurological abnormalities that could explain his back pain, contrast-enhanced computed tomography (CT) showed abnormal retroperitoneal lesions (Fig. 1 A, B) and consequent bilateral hydronephrosis. Palliatively, ureteral stenting was put, then his back pain was ameliorated. Laboratory tests showed normal serum IgG4 (71 mg/DL), and laparoscopic biopsy showed fibrosis with perivascular CD20+ and CD3+ lymphocyte infiltration(Fig. 1 E, F, G), similar to the previous report of idiopathic retroperitoneal fibrosis [3]. In addition, with no IgG4-positive cells, infections, granulomas, or malignancies, idiopathic retroperitoneal fibrosis was diagnosed. Standard steroid therapy (prednisolone 1 mg/kg) [4] for retroperitoneal fibrosis was not selected due to the history of severe obesity and emotional disturbance. Therefore, the optimal treatment for idiopathic retroperitoneal fibrosis complicated with MS was unclear. However, we took noticed the reports of rituximab (anti-CD20 antibody) that have therapeutic evidence for retroperitoneal fibrosis [5]. In addition, we reviewed the inadequate MS management in recent clinical courses: two times of relapses last two years, and the expanded disability status scale was 4.0. Because rituximab for MS or retroperitoneal fibrosis was not approved by health insurance in Japan and the patients did not choose the rituximab, we changed disease modifying drug (DMD) from dimethyl fumarate to ofatumumab (20 mg, for weeks 0, 1, and 2 followed by subsequent monthly dosing, starting at week 4) based on the two facts that ofatumumab is also an anti-CD20 monoclonal antibody (mAb) and high-efficacy consensus therapy for MS. Two months later, the CT scan showed a significant improvement in retroperitoneal fibrosis (Fig. 1 C, D) without any other immunological therapy. In addition, there have been no relapses of MS.

2. Discussion

Recently, the involvement of CD20-positive lymphocytes in the development of MS has been identified, and anti-CD20 mAb such as ofatumumab has become the consensus therapy [6,7]. On the other hand, it is also evident that the pathogenesis of retroperitoneal fibrosis is strongly based on CD20+ lymphocytes [3], which was also shown in the perivascular CD20+ lymphocytes of the present case's retroperitoneal fibrosis. Based on previous reports, ofatumumab, anti-CD20 mAb, might be one of the most promising monotherapies for both diseases. However, there have been no reports of retroperitoneal fibrosis treated by ofatumumab.

Fortunately, ofatumumab for MS was simultaneously effective for idiopathic retroperitoneal fibrosis. This novel observation cannot be explained by other factors because there have been no reports of interferon or dimethyl fumarate-induced retroperitoneal fibrosis, and spontaneous remission was reported to be rare [8]. On the other hand, it is clinically important that ofatumumab was administered at a significantly low dose than rituximab in retroperitoneal fibrosis. In rituximab reports, the dose for retroperitoneal fibrosis was nearly equivalent to that for hematologic diseases [5]. In contrast, ofatumumab for MS in the present case was only 20 mg/month, which was one hundredth, compared to 2000 mg/month of ofatumumab for hematologic diseases [9]. Therefore, ofatumumab appeared to be more effective than rituximab. This possible superiority of ofatumumab over rituximab may be based on its stronger affinity for CD20+ B cells [9,10], and it could be translated into various autoimmune diseases like rheumatoid arthritis

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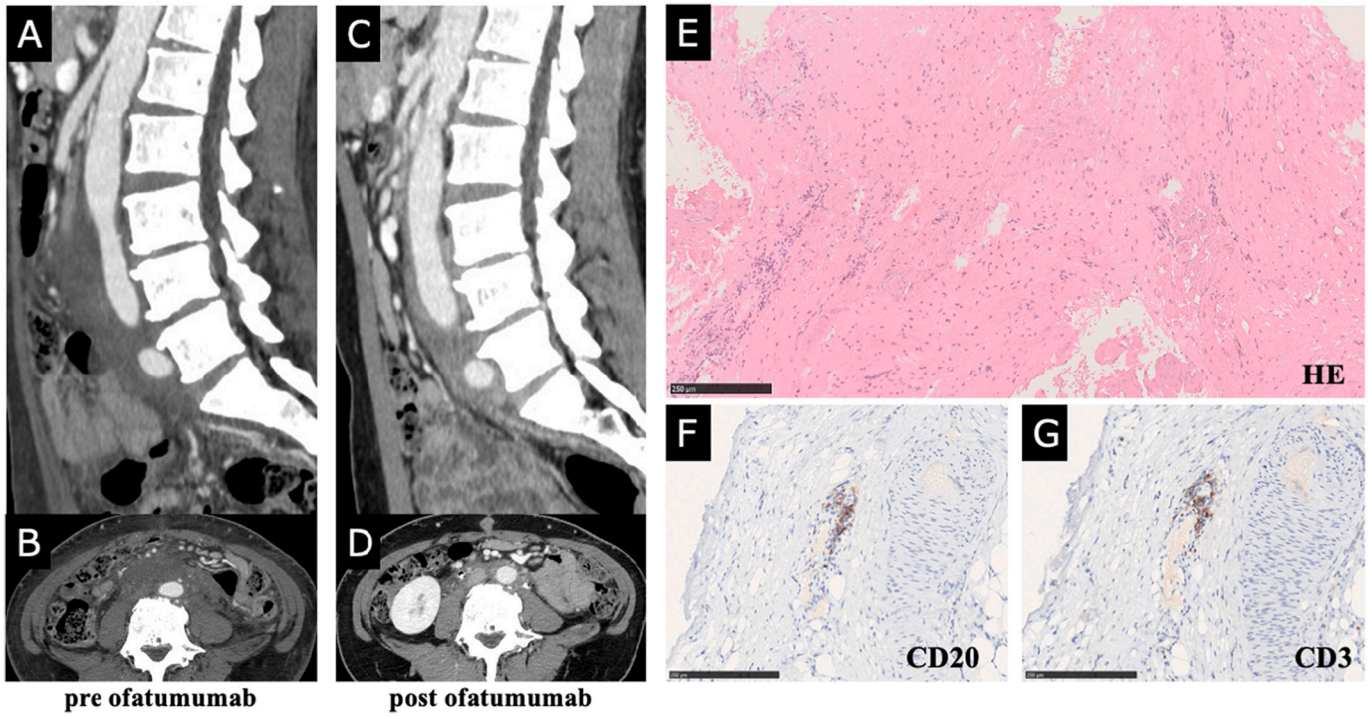

Fig 1. Before the use of ofatumumab, enhanced computed tomography shows thick retroperitoneal fibrosis and compressed, flattened aorta (A, B). After two month-use of ofatumumab, the fibrosis is reduced and the aorta shape becomes normalized (C, D). Histopathology of hematoxylin-eosin (HE) staining shows retroperitoneal fibrosis (E). Immunostaining shows perivascular CD20+ and CD3+ lymphocytes in retroperitoneal fibrosis (F,G). All scale bar 250 μm.

that were reported to be curative with rituximab [1]. In addition, because recent reports indicate that most "idiopathic" retroperitoneal fibrosis may have a similar etiology and therapeutic response to IgG4-related disease [5], ofatumumab for MS might be also applicable to concomitant IgG4-related disease [11]. Therefore, there may be other unnoticed autoimmune diseases that can be treated simultaneously with doses of ofatumumab for MS.

3. Conclusion

The dose of ofatumumab as a DMD for MS improved idiopathic retroperitoneal fibrosis simultaneously, and this was the first case treating idiopathic retroperitoneal fibrosis by ofatumumab.

Authors' contributions

A. Hanazono, Y. Sanpei, H. Shimada, K.Yasuda, Y.Takahashi, H. Funasaka, and M.Sugawara contributed to the study design and drafted the manuscript. R. Sagehashi, Y. Hiroshima and H.Nanjo diagnosed retroperitoneal fibrosis and revised the manuscript. All authors critically read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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