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CLINICAL CASE

Demyelinating brain lesions in a Crohn's patient under adalimumab

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KEYWORDS
Demyelination;
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Abstract Demyelinating conditions of the central nervous system can be associated with inflammatory bowel disease, but since the introduction of tumour necrosis factor antagonist therapies, a number of cases of demyelinating disease associated with the treatment are being described.

We report the case of a 36-year-old female, with Crohn's disease, treated with adalimumab for eighteen months. She developed severe headache and the investigations disclosed several demyelinating lesions in the sub cortical white-matter of the frontal and parietal lobes. The suspension of adalimumab resulted in symptomatic relief in a few weeks, but the brain lesions persisted after eight months of follow-up.

The cause of these lesions in inflammatory bowel disease patients treated with tumour necrosis factor antagonists is not yet clearly established, but a raised awareness to this possibility is important, as an early change of treatment is recommended.

PALAVRAS-CHAVE
Desmielinização;
Doença de Crohn;
Adalimumab

Lesões cerebrais desmielinizantes em doente com doença de Crohn sob adalimumab

Resumo As lesões desmielinizantes podem ocorrer na doença inflamatória intestinal, mas, desde a introdução das terapêuticas com antagonistas do factor de necrose tumoral, os casos de lesões desmielizantes associados ao tratamento têm vindo a ser cada vez mais descritos.

Descrevemos o caso de uma mulher de 36 anos, com doença de Crohn, tratada com adalimumab durante dezoito meses. Desenvolveu cefaleias intensas cuja investigação levou ao achado de lesões desmielinizantes na substância branca frontal e parietal. A suspensão do adalimumab levou a rápida melhoria sintomática, mas as imagens das lesões encefálicas persistiram inalteradas oito meses depois.

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A causa destas lesões não está definitivamente estabelecida e o seu mecanismo é complexo; é importante considerar precocemente esta possibilidade em doentes tratados com antagonistas do factor de necrose tumoral, pois recomenda-se uma mudança da estratégia terapêutica nestas situações.

Introduction

Inflammatory bowel disease (IBD) is often associated with a variety of extra-intestinal manifestations; among these, neurological and neuromuscular manifestations are well known.[1,2] They can result from the disease itself, by nutrient malabsortion, by thromboembolic events or by changes in immunologic processes. They can also be related to treatment, either as a side effect of medication or as an infectious consequence of immunosuppression.

Peripheral neuropathy and cranial nerve lesions can occur in IBD,[3–6] and nerve demyelination is considered to result from ischemia related to hypercoagulation or vasculitis. On the other hand, the central nervous system (CNS) can be involved in up to 4% of IBD patients,[7] often with cerebrovascular disease also caused by vasculitis, by thrombosis or by haemorrhage related to coagulopathy. Clinical patterns of multiple sclerosis are also associated to IBD,[8–10] either before or after its diagnosis. The number of those cases is small, so it is not clear if a causal relationship exists, or if there is an increased susceptibility to multiple sclerosis in IBD patients.[11] Moreover, the differential diagnosis between multiple sclerosis and CNS vasculitis in an IBD patient can be difficult, thus reducing the number of reported patients with a correct diagnosis.

We report the case of a Crohn's disease patient with demyelinating brain lesions associated with the use of tumour necrosis factor α antagonists (anti-TNF).

Case report

A 35-year-old Caucasian female was referred to the gastroenterology outpatient clinic because of diarrhoea. Crohn's disease was diagnosed at another hospital six years before, after an ileocolonic resection for acute ileitis. She was on oral mesalazine, and she complained of frequent diarrhoea without blood, sometimes with abdominal pain, relieved by oral prednisolone for short periods of time. These symptoms were well tolerated, her weight was stable and she denied fever or loss of appetite. She was a non-smoker, she denied any neurological symptoms and no relevant diseases were found in her past and familial history. Physical exam showed a patient in a good nutritional status, with normal body temperature and blood pressure. Skin and oral mucosa were normal, and so was the cardiopulmonary examination. The abdominal examination disclosed a median laparotomy scar and a painless ovoid 10 cm mass could be felt by palpation in the deep right lower quadrant. The initial blood tests were within normal range, including the ESR and the C-reactive protein. Oral budesonide 3 mg tid was started, followed later by oral azathioprine 100 mg/day, later increased to 150 mg/day.

The symptoms markedly improved and five months later a MRI enterography did not find signs of active inflammation. Two bouts of diarrhoea and abdominal pain needing oral corticosteroids occurred in the following months and a decision to start anti-TNF treatment was made. As no contraindications were present, subcutaneous adalimumab was started and, after the induction, the patient remained on 40 mg of adalimumab every other week. Eighteen months after the start of the anti-TNF treatment, the patient was free of corticosteroid use, azathioprine had been stopped, influenza immunization had been given and only two short bouts of diarrhoea had occurred, easily managed with symptomatic medication. Laboratory evaluation showed slight normocytic normochromic anaemia, with a haemoglobin value of 10.9 g/dL, with all the other laboratory findings within normal limits.

After eighteen months of adalimumab treatment the patient complained of diffuse headache, gradually more intense, without photophobia, visual impairment, fever, dizziness, nausea or vomiting. There was no muscle or joint pain, and no skin lesions were present. The neurological evaluation was normal, without signs of meningitis or peripheral neuropathy. Blood white and red cell counts were normal, ESR was 46 mm at 1 h, C-reactive protein was 0.9 mg/mL. Antinuclear antibody was positive up to a dilution of 1/360, but other autoantibodies and serologic markers suggesting vasculitis were absent.

Brain CT showed small hypodense lesions in the frontal white-matter subcortical layer, suggesting demyelinating lesions. MRI revealed several demyelinating lesions in the white-matter of both hemispheres, showing as hypersignal in protonic and T2 density, with different sizes and rounded shapes (Fig. 1). Their topography was subcortical, both frontal and parietal. These lesions were suggestive of demyelinating lesions related to chronic small-vessel ischemia. The eco-Doppler study of the large neck arteries failed to show any abnormalities and the patient declined a spinal tap.

Adalimumab was stopped and a progressive symptomatic relief was evident along the next two months. Immunossupression with azathioprine was restarted at 150 mg/day and no IBD flares were noted during the eight months of follow-up. Despite the clinical improvement a second MRI confirmed the persistence of the white-matter lesions.

Discussion

Our patient had an ileal Crohn's disease with inflammatory phenotype, already submitted to surgical resection and

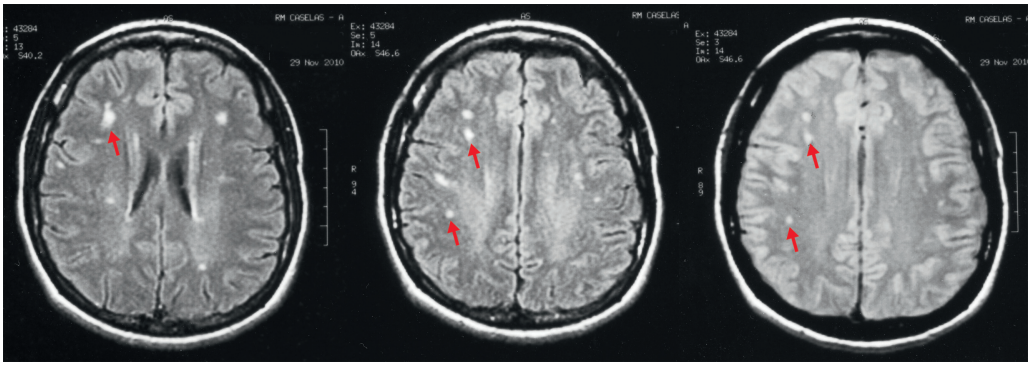

Figure 1 Brain MRI showing small rounded lesions (arrows) in the subcortical white-matter of both hemispheres.

needing frequent systemic corticosteroids. The indication for anti-TNF therapy was clear, and as absence from work could be a problem, adalimumab was the patient's option with satisfactory clinical and radiologic evolution of the intestinal disease.

Neurologic symptoms started eighteen months after treatment. The CNS lesions suggested a demyelinating condition similar to multiple sclerosis, but the possibility of an IBD-associated vasculitis was also considered, especially taking in account the MRI images. However, clinical findings of primary vasculitis were absent, namely fever, muscle pain, arthritis, skin lesions, peripheral neuropathy or signs of renal lesion. Chest radiograph, serum creatinine, liver and muscle enzymes and urinary sediment were normal. Viral serologies were negative, and autoantibodies titers were low, excepting the antinuclear antibody titer that was positive at 1/360 dilution – but an isolated high antinuclear antibody titer is frequent in patients on anti-TNF therapy,[12] and can even occur in normal persons. In addition, primary CNS vasculitis is rare, and systemic vasculitis with brain involvement would be expected to cause larger lesions.[13]

The use of anti-TNF in the treatment of IBD represented a major therapeutic advance, allowing significant benefits in the induction and maintenance of remission in Crohn's disease. However, in spite of an adequate evaluation and selection of patients, important complications can occur, some of them involving the CNS. Anti-TNF associated CNS lesions have been reported in IBD, related both to the use of infliximab or adalimumab[14]; it is a matter of debate if those lesions are a direct consequence of the treatment, or if the treatment just uncovers a subclinical demyelinating condition.

The demyelinating lesions associated to the anti-TNF therapy are infrequent but their early detection is important, so all neurological symptoms in these patients must be carefully evaluated at any point during the course of the treatment. The postulated mechanism for the lesions involves the activation of myelin-specific T cells; these cells would migrate into the CNS thus causing the lesions. The more frequent complaints are related to paresthesia, headache, confusion and visual or gait impairment.[15] Severe forms of Guillain-Barré syndrome are also reported. These manifestations can occur when the treatment starts or many months after the beginning of the therapy. A CNS MRI will show a pattern of white-mater lesions similar of those found in multiple sclerosis.[16] The precise evaluation of these finding may be difficult taking in account the reported occurrence of similar findings in IBD patients not treated with anti-TNF and even in normal controls[17] – although other studies have found those lesions to be much less frequent.[18] The use of MRI angiography of the CNS or the study of the cerebrospinal fluid may be helpful in selected cases.

The clinical trials with adalimumab reported demyelinating disease in 0.2% of the 3160 patients treated up to 2009,[19] but in spite of this low incidence we have considered an association between adalimumab treatment and demyelinating lesion in our patient.

The headache complaints began six weeks after the anti-influenza vaccination, and a hypothetic relation between the two events was considered. Despite a few reported cases associating the two events, anti-influenza vaccination is not considered a cause of demyelination, and does not cause symptoms in patients with subclinical disease.[20] Moreover, the National Multiple Sclerosis Society considers that the seasonal influenza vaccination for 2010–2011, which covers H1N1 strain, is safe and should be administered to multiple sclerosis patients even when those patients are under treatment with interferon or natalizumab.[21]

As soon as the white-matter demyelinating lesions are found, cessation of anti-TNF treatment is recommended as this leads to an improvement in most patients.[1] However the course of the neurological manifestations is unpredictable in each individual case.[22] In agreement with published reports and recommendations,[19] anti-TNF therapy was suspended. The option for azathioprine was based on the need to maintain an adequate immunosuppression. The possibility of switching to infliximab was discussed, but the anti-TNF associated demyelinating lesions are considered a class effect (G. Van Assche, personal communication) and this option has no support from the published literature.

There was a temporal relation between the symptomatic improvement of our patient and the adalimumab cessation, and the patient regained a stable clinical condition that allowed her to keep her usual daily activities. Neurological signs or symptoms are not expected in the future, but so far we cannot definitely exclude the possibility of a subclinical multiple sclerosis unmasked by the exposure to anti-TNF, so the patient is still under surveillance at the neurology outpatient clinic.

This case report reminds us of the possible occurrence of neurological lesions in IBD patients, especially in those on

anti-TNF treatment. An early detection and the immediate treatment change can prevent irreversible lesions or severe neurological impairment.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Zois CD, Katsanos KH, Kosmidou M, Tsianos EV. Neurologic manifestations in inflammatory bowel diseases: current knowledge and novel insights. J Crohns Colitis. 2010;4:115–24.
2. Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Medicine (Baltimore). 1976;55:401–12.
3. Gondim FA, Brannagan 3rd TH, Sander HW, Sander HW, Chin RL, Latov N. Peripheral neuropathy in patients with inflammatory bowel disease. Brain. 2005;128:867–79.
4. van de Scheur MR, van der Waal RI, van Bodegraven AA, Völker-Dieben HJ, Starink TM, van der Waal I. Cheilitis granulomatosa and optic neuropathy as a rare extra-intestinal manifestation of Crohn's disease. J Clin Gastroenterol. 2002;34: 557–9.
5. Akbayir N, Caliş AB, Alkim C, Sökmen HM, Erdem L, Ozbal A, et al. Sensorineural hearing loss in patients with inflammatory bowel disease: a subclinical extra-intestinal manifestation. Dig Dis Sci. 2005;50:1938–45.
6. Lloyd DA, Payton KB, Guenther L, Frydman W. Melkersson-Rosenthal syndrome and Crohn's disease: one disease or two? Report of a case and discussion of the literature. J Clin Gastroenterol. 1994;18:213–7.
7. Lossos A, River Y, Eliakim A, Steiner I. Neurologic aspects in inflammatory bowel disease. Neurology. 1995;45: 416–21.
8. Scheid R, Teich N. Neurologic manifestations of ulcerative colitis. Eur J Neurol. 2007;14:483–93.
9. Purrmann J, Arendt G, Cleveland S, Borchard F, Fürst W, Gemsa R, et al. Association of Crohn's disease and multiple sclerosis. Is there a common background? J Clin Gastroenterol. 1992;14:43–6.
10. Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. Gastroenterology. 2005;129:819–26.
11. Thomas CW, Weinshenker BG, Sandborn WJ. Demyelination during anti-tumour necrosis factor α therapy with infliximab for Crohn's disease. Inflamm Bowel Dis. 2004;10:28–31.
12. Beigel F, Schnitzler F, Laubender RP, Pfennig S, Weidinger M, Göke B, et al. Formation of antinuclear and double strain DNA antibodies and frequency of lupus-like syndrome in anti-TNFα antibody treated patients with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17:91–8.
13. Thomas Jr CW, Weinshenker BG, Sandborn WJ. Demyelinization during anti-tumour necrosis factor alpha therapy with infliximab for Crohn's disease. Inflamm Bowel Dis. 2004;10:28–31.
14. Andersen NN, Caspersen S, Jess T, Munkholm P. Occurrence of demyelinating diseases after anti-TNFα treatment of inflammatory bowel disease: a Danish Crohn's Colitis Database study. J Crohn's Colitis. 2008;2:304–9.
15. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, et al. Demyelination occurring during anti-tumour necrosis factor therapy for inflammatory arthritides. Arthritis Rheum. 2001;44:2862–9.
16. Polman CH, Rheingold SC, Edam G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the ''Mc Donald criteria''. Ann Neurol. 2005;58:840–6.
17. Geissler, Andus t, Roth M, Kullmann F, Caesar I, Held P, et al. Focal white-matter lesions in brain of patients with inflammatory bowel disease. Lancet. 1995;345:897–8.
18. Hart PE, Gould SR, MacSweeney JE, Clifton A, Schon F. Brain white-matter lesions in inflammatory bowel disease. Lancet. 1998;351:1558.
19. Colombel JF, Sandborn WJ, Panaccione R, Robinson AM, Lau W, Li J, et al. Adalimumab safety in global clinical trials of patients with Crohn's disease. Inflamm Bowel Dis. 2009;15:1308–19.
20. DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, et al. Vaccination and risk of central nervous system demyelinating disease in adults. Arch Neurol. 2003;60:504–9.
21. http://www.nationalmssociety.org/living-with-multiple-sclerosis/healthy-living/vaccinations/index.aspx [accessed 01. 09.11].
22. Lozeron P, Denier C, Lacroix C, Adams D. Long term course of demyelinating neuropathies occurring during tumour necrosis factor-α-blocker therapy. Arch Neurol. 2009;66:490–7.