GÓLLEIN-BARRE AND MILLER FISHER SYNDROMES IN ULCERATIVE COLITIS TREATED WITH INFliximab

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ABSTRACT

We present the case of one 64 years old woman with long-standing ulcerative colitis, which was treated intermittently with steroids and immunosuppressives (mainly azathioprine) for controlling both the flare-ups and also for maintaining in remission of her inflammatory bowel disease. After partially losing the response to these drugs, she was treated with biologics, mainly infliximab (anti-TNFα) during several months, and she developed a florid picture of Guillain-Barré and Miller Fisher syndromes, that was probably related to the use of this drug. Her evolution was good and she is recovering slowly of her neurological affectionation. Taking into account this clinical association we performed a review of the previously described cases with other rheumatic or autoimmune diseases including Crohn’s disease, but not with ulcerative colitis.

Key words: Guillain-Barre syndrome, Miller Fisher syndrome; ulcerative colitis, infliximab, treatment

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acquired inflammatory peripheral neuropathy of unknown origin and it is the most frequent cause of acute or subacute flaccid paralysis. Its clinical course is usually monophasic, with partial or complete recovery. It is considered to be probably of autoimmune origin. In around 60% of the cases, there is an previous acute respiratory or gastrointestinal infection. GBS comprises a heterogeneous group of conditions defined by varying clinical, electrophysiologic and pathologic features.

The relationship between inflammatory bowel disease (IBD) and peripheral neuropathy has been described since 1985, both in individual as in descriptive studies. Peripheral neuropathy (PN) in IBD patients has been reported as individual cases or small series; however, its clinical and electrodiagnostic features have not been well characterized. The
PN syndromes in IBD patients are diverse. Demyelinating forms may occur at any time, but at the onset of the disease and the pure sensory neuropathy is more common. Response to immunotherapy may occur in both demyelinating and axonal neuropathies\textsuperscript{2-7}.

We present the case of one patient with a severe outbreak of ulcerative colitis (UC) treated with infliximab (IFX) that developed a Miller Fisher Syndrome (MFS). This later one variant of GBS, which comprises between 3-5\% of cases in western countries, and is characterized by the triad of ataxia, external ophtalmoplegia and areflexia. Antibodies to ganglioside GQ1b are detected in 80-90\% of patients\textsuperscript{8}. We have identified at least 16 patients in the FDA\’s post marketing database in whom GBS developed following TNF\textsubscript{\alpha} antagonist therapy.

**CASE REPORT**

We present the case of a 64-year-old woman, diagnosed of ulcerative proctitis in 1980, with moderate outbreaks of left inflammatory colitis, treated with 5-aminosalicylates (5-ASA) and oral corticoids with poor adherence. She presented recently, a severe clinical outbreak in 2006. An endoscopic exploration confirmed the presence of multiple ulcerations on the left colon being diagnosed of left UC. Treatment with infliximab (IFX) was started in 2006 at the usual dose (5mg/Kg) every two months during 3 years, until her admission. She was hospitalized because of relapse. One week before admission the patient presented flu symptoms associated with inability to walk with repeated fallings, with progressive deterioration of her motor symptoms in the last 72 hours, accompanied by fluctuating confusional episodes, ophthalmpoplegia, and dysarthria.

On physical examination, her chin showed post-traumatic ecchymosis, mouth rhagades, and nystagmus in intermediate and extreme positions of the gaze, associated with dysarthria and loss of orientation temporo-spatial. The abdomen was mildly distended, without signs of peritoneal irritation. She presented a motor deficit in all the extremities, with loss of force in the upper limbs: proximal: 4/5 and distal 3-4/5, and in the lower extremities: Proximal: 5/5 and Distal: 4-5/5, as well as difficulty to stand without assistance, due to affectation of the pelvic muscles. Besides she reported painful dysesthesia and hypoesthesia in feet and fingers, all stretch reflexes were absent and the plantar reflex showed bilateral an upward response.

Blood analysis showed iron deficiency anemia: Hemoglobin: 82 g/l, Hematocrit: 0.231/l; MCV: 88 fl; Leukocytes: 18.5 x10\textsuperscript{12}/L (89\% neutrophiles); Platelets: 351 x 10\textsuperscript{12}/l, ESR: 98 mm/h, CRP: 9.6 mg/dl (normal < 0.50);Glucose, Creatinine, Uric acid, Calcium, LDH, AST, ALT, GGT, AP, Total Bilirubin, Cholesterol and Triglycerides, were normal. Folate: 2.7 ng/ml, Ferritin: 3.116 ng/ml (15-200), Transferrin: 9.8 g/l (1.93-3.08), TSI: 56.4\%, Prealbumin: 10.4 mg/dl (17-42 mg/dl). Parasite search in stools, serological screening for viral infections, *Campylobacter jejuni* and *Borrelia burgdorferi* and IgM-antibodies anti-gangliosides GM-1, GDA-1 and GM-2, were all negative. The cerebrospinal fluid (CSF) was acellular ; glucose levels, 45 mg/dl (50-80 mg/dl), with increased proteins, 119 mg/dl (normal < 40 mg/dl).

Cerebral computed tomography (cCT) and cranial magnetic resonance imaging (cMRI) were normal. The abdomino-pelvic CT showed circumferential and symmetrical thickening of the wall of the total colon, in relation with the reactivation of her IBD.
The colonoscopy confirmed the presence of a moderate-severe ulcerative colitis, confirmed by the histologic findings of a diffuse inflammatory reaction accompanied by cryptic abscesses in the lamina propria. Neurophysiologic studies confirmed the presence of a sensitive-motor polyneuropathy with mixed characteristics and of moderate degree. Four months later they continued showing a diffuse sensory nerve conduction loss (sNCS) of both legs. During her stay she received basic treatment of the outbreak of the UC with intravenous corticoids at doses of 1 mg/kg/day of prednisolone. After establishing the diagnosis of GBS, she received a cycle of intravenous immunoglobulin (IVIG) at a dose of 0.4 g/kg/day during 5 days. The patient's progress has been though slow up to complete recovery of the neurologic symptoms and the outbreak of ulcerative colitis, declining gradually the doses of steroids to the point of its withdrawal and suspension of infliximab. The patient is currently staying stable, being administered a combination therapy of oral 5-ASA (2g/day) and azathioprine (100 mg/day).

A written informed consent was given by the patient in order to publish her case.

DISCUSSION

Ulcerative colitis (UC) and Crohn's disease (CD) have been considered traditionally as processes limited to the digestive tract, but they are also associated to numerous extra-intestinal manifestations (EIM), characterized by the involvement of various systems, both in direct relationship with the clinical evolution of IBD, as independent of the clinical course of IBD. The EIM appear in 25 - 30% UC patients. Furthermore, the presence of these EIM varies depending on the geographic area, location of the lesions, duration and type of treatment of the disease. The most frequent affectations are cutaneous, rheumatologic, ophthalmic, hepatobiliary and genito-urinary. The prevalence of peripheral neuropathy (PN) in patients with IBD, varies largely. In a retrospective study the ranges were between 0.9 - 3.6 % in CD patients. In prospective studies, once other secondary polyneuropathies are excluded, the prevalence ranges between 1.9 - 13.4 % 1-6. These differences are attributed to genetic differences and patient selection. They seem to be more frequent in UC than in CD, with an estimated average incidence of 1.9 %.

Clinical expressivity differs greatly and accordingly they are classified in polyneuropathies that are or sensory and/or motor, autonomic or mixed, axonal or demyelinating, or classified by its duration as acute and chronic. Additionally, several mononeuritides, brachial and cranial neuropathies have been published. Up to nine different mechanisms have been postulated by which IBD, can affect the peripheral nervous system that could act alone, or in combination such as: 1/ Malabsorption of trace elements, together with the disease severity, or hypovitaminosis, in relation to aminosalicylates therapy. 2/ Production of toxic and metabolic agents. 3/ Associated infections as a complication of immunosuppression like C. Jejuni, for instance 4/ Side-effects of the treatment, such as neurotoxicity mediated by the prolonged treatment with methotrexate. In this case, they tend to be reversible after stopping the drug. 5/ Associated thromboembolism. 6/ Immunological alterations. 7/ Vasculitis of the vessels that nourish the peripheral nerves. 8/ Alterations of the coagulation like mutation of
<table>
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<tr>
<th>Author Ref, Year</th>
<th>Age (y.o) sex</th>
<th>Indication</th>
<th>Treatment</th>
<th>Clinical manifestation</th>
<th>Medical history</th>
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<tr>
<td>Shin In-Sook et al. Arthritis Rheumatism 2006</td>
<td>56 Male</td>
<td>RA</td>
<td>Infliximab 15 months</td>
<td>Ataxia, Dysarthria, Tetraparesis, Areflexia</td>
<td>Influenza vaccine</td>
<td>Demyelinating Polineuropathy</td>
<td>IVIG</td>
<td>Steroids</td>
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<td>Mohan N. et al. Arthritis Rheumatism 2001</td>
<td>49 Female</td>
<td>Crohn</td>
<td>Infliximab Several years</td>
<td>Muscle weakness, R</td>
<td>Flu symptoms</td>
<td>Demyelinating Polineuropathy</td>
<td>IVIG</td>
<td>Not specified</td>
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<tr>
<td>US-FDA Annual Report 2003</td>
<td>66 Female</td>
<td>RA</td>
<td>Infliximab 8 months</td>
<td>Symmetrical muscle weakness</td>
<td>Lower Respiratory infection</td>
<td>Not specified</td>
<td>IVIG</td>
<td>Not response</td>
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<td>US-FDA Annual Report 2003</td>
<td>50 Female</td>
<td>RA</td>
<td>Infliximab 6 months</td>
<td>Progressive Ascending Tetraparesis</td>
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<td>IVIG</td>
<td>Partial recovery after 2 weeks</td>
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<tr>
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<td>43 Male</td>
<td>Psoriatic Arthritis</td>
<td>Infliximab 5 months</td>
<td>Ascending Tetraparesis</td>
<td>Not specified</td>
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<td>Not Specified</td>
<td>Partial recovery After 2 weeks</td>
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<td>US-FDA Annual Report 2003</td>
<td>62 Male</td>
<td>RA</td>
<td>Infliximab 5 months</td>
<td>Ascending Paraparesis</td>
<td>FUO</td>
<td>Not specified</td>
<td>Plasmapheresis MV</td>
<td>Partial recovery after 10 months</td>
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<tr>
<td>Casternas M et al. Arthritis Rheumatism 2002</td>
<td>34 Male</td>
<td>Psoriatic Arthritis</td>
<td>Infliximab 3.5 months</td>
<td>Ascending Paraparesis</td>
<td>Upper Respiratory Infection</td>
<td>Demyelinating Polineuropathy</td>
<td>IVIG</td>
<td>Complete Recovery after 3 weeks</td>
</tr>
<tr>
<td>US-FDA Annual Report 2003</td>
<td>81 Female</td>
<td>RA</td>
<td>Infliximab Unknown time</td>
<td>Weakness, Paresthesia Limited Diaphragmatic function</td>
<td>Not specified</td>
<td>Not specified</td>
<td>IVIG</td>
<td>Plasmapheresis</td>
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<tr>
<td>US-FDA Annual Report 2003</td>
<td>58 Female</td>
<td>RA</td>
<td>Etanercept 2 years</td>
<td>Progressive Ascendent Paralysis Paresthesia in face and arms</td>
<td>Flu symptoms</td>
<td>Not specified</td>
<td>IVIG</td>
<td>Steroids Recurrences During 6 months</td>
</tr>
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Table 1. Clinical characteristics of the GBS in patients treated with monoclonal antibodies.
factor V of Leiden 9/ Autoimmunity as indicated by the association between GBS and IBD 4-7.

Tumor necrosis alpha (TNF-α) factor plays an important role as a mediator of inflammation in IBD, in the presence and intensity of extra-intestinal manifestations of the UC as uveitis and spondyloarthritis. Infliximab, a chimerical monoclonal antibody against TNF-α, is effective in the induction and maintenance of the remission of UC7-8. Various adverse effects have been described associated with the administration of this drug, such as reactivation of latent infections (mainly tuberculosis), demyelinating lesions, optic neuritis, transverse myelitis, GBS and chronic polyneuropathies7-8. The FDA has warned about the neurologic complications which appeared in 17 patients taking TNF-α antagonist drugs, 11 patients received Etanercept, 5 Infliximab and one Adalimumab 7. The inflammatory role of the TNF-αin patients diagnosed of GBS has been confirmed, finding its levels elevated to up to 63% in the sera of these patients, presenting a direct correlation between the degree of the clinical activity and the electrophysiological severity of the illness8. Its normalization, took place after the clinical recovery of the disease.

TNF-α deficiency causes a disturbance in the regression of the reactivity of the T cells specific of myelin. Blocking the endogenous TNF-α increased serum levels in patients treated with monoclonal antibodies, would lead to an improvement in the proliferative response linked to T cells and the production of other cytokines. The prolonged administration of these drugs improves the autoimmune responses by enhancing the signal mediated by the T cell receptor and the decrease of the apoptosis of auto-reactive T cells 7-8. Therefore, even small doses of anti-TNF-α agents, prolongs the response of T cells specific for myelin capable of causing a immuno-mediated neuropathy 9. Treatment with anti-TNF-α drugs, can promote the development of the GBS, increasing the number of peripheral T cells, or alternating the intrinsic balance of TNF-α and its receptors in the compartment of the peripheral nervous system. These factors alone or in combination can induce a clinical expression in patients immuno-genetically susceptible 9.

Our patient had received treatment with Infliximab for 3 years time before developing the GBS. In her case, the development and course of the extra-intestinal manifestation has had correlation with the activity of the UC what possibly indicates that UC could have been responsible for the GBS and treatment with infliximab may has acted as an enhancer in the presence of neurological pathology. We ought to remind the recommendations of the British Society of Rheumatology (BSR), respecting the prescription of monoclonal antibodies against TNF-α. They recommend to avoid the use of these agents in patients with pre-existing demyelinating diseases. In patients without such previous complications, they suggest the withdrawal of the drug should any neurologic impairment occur in a temporal relationship to its administration 10.

We summarize the clinical characteristics of the GBS cases previously described in patients treated with monoclonal antibodies (Table 1).

CONCLUSION

This is a new case report of the association of GBS and MFS occurring with tumor necrosis factor α antagonist therapy in one patient with ulcerative colitis and to our knowledge it is the first description reported in this disease.
COMPETING INTERESTS

The authors certify that they do not have any actual or potential conflict or competing interest.

REFERENCES