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Acute motor sensory polyneuropathy (AMSAN) complicating active ulcerative colitis with a patchy distribution

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Abstract

We report a case of acute motor and sensory neuropathy during a flare of ulcerative colitis. A 28-year-old male presented with a flare of distal ulcerative colitis despite treatment with mesalamine enemas and suppositories simultaneously with rapidly deteriorating weakness and needle sensation in both legs. Neurological assessment showed axonal sensorimotor polyneuropathy affecting mainly the lower limbs and to a lesser extent the upper limbs. Colonoscopy revealed moderately to severe active ulcerative colitis with a patchy distribution involving the rectum and the right colon. Vitamin and folic acid levels were normal. Virological, immunological and other laboratory tests were negative except for positive anti-ganglioside antibodies (anti-GM1). Ulcerative colitis and polyneuropathy improved when patient was treated with immunosuppressive therapy (corticosteroids, immunoglobulin and azathioprine). Peripheral polyneuropathy is a rare extraintestinal manifestation of ulcerative colitis and it is probably associated with an autoimmune pathogenetic mechanism. (Acta gastroenterol. belg., **2006**, 69, **226-230**).

Key words : extraintestinal complications, endoscopic patchiness, polyneuropathy, ulcerative colitis.

Abbreviations

Anti-ganglioside Antibodies (anti-GM1) ; Crohn's Disease (CD) ; Chronic Inflammatory Demyelinating Neuropathy (CIDP) ; Inflammatory Bowel Disease (IBD) ; Magnetic Resonance Imaging (MRI) ; Peripheral Neuropathy (PN) ; Ulcerative Colitis (UC).

Introduction

Ulcerative colitis (UC) is characterized by a chronic inflammatory process affecting the mucosa of the large bowel. Traditionally, UC is described as a disease which always involves the rectum and may spread to more proximal portions of the colon in a continuous fashion without skip areas (1). However, in some cases the inflammation (endoscopic and /or histological) in UC may be presented with a patchy distribution with or without rectal sparing (1-4).

Extraintestinal manifestations occur in 25% to 30% of patients with UC and are more prevalent in patients with extensive disease (5-8). Neurologic complications are rare extraintestinal manifestations in patients with UC (~3%), including peripheral neuropathy (PN), myelopathy, myopathy, seizures and cerebrovascular disease (9,10).

We report a case of a 28-year-old male who developed acute axonal peripheral sensorimotor polyneuropathy during a flare of ulcerative colitis which was found to involve the distal left and the proximal colon separated by uninvolved sigmoid and descending colon (patchy distribution with "skip" areas).

Case report

A 28-year old, Caucasian male, with a history of distal left-sided ulcerative colitis restricted to the rectum, presented at our outpatient clinic complaining for bloody diarrhoeas (4 bowel movements per day including nocturnal diarrhoea) and tenesmus during the last 2 months despite being treated with mesalamine enemas and suppositories. He also pointed out that he was taken to the hospital by a friend, because he was suffering from pain and needle sensations in both legs with progressive worsening accompanied by inability to walk without support.

The patient presented for the first time 11 months earlier at the outpatient clinic of our Department complaining for bloody diarrhoeas. Ulcerative proctitis of moderate endoscopic severity, with mucosal redness, oedema, friability and multiple erosions confined at the distal rectum in a continuous fashion, was noted in flexible sigmoidoscopy and multiple biopsies were taken. Histological examination of the biopsies was suggestive for active chronic ulcerative proctitis with mucosal neutrophilic infiltration, crypt abscesses, depletion of goblet cells, erosions, and crypt distortion. He was treated with mesalamine suppositories with clinical improvement, but 8 months later the patient discontinued the suppositories because of absence of symptoms. One month later, he presented with a new flare of the disease. Sigmoidoscopy at that point revealed findings of severe ulcerative colitis, with mucosal redness, oedema, friability and multiple erosions, extending to the rectum, with

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normal mucosal appearance proximal to the rectosigmoid junction in sigmoid and descending colon. Topical treatment with mesalamine suppositories plus mesalamine enemas for active distal ulcerative colitis was started again. Simultaneously he presented numbness and weakness in the legs rapidly deteriorating and he was admitted to the hospital.

He was a non-smoker, and he did not take any other medication, including metronidazole.

The patient was slender (Body Mass Index of 19), his vital signs on admission were normal and physical examination, except for the neurologic signs, was unremarkable. Routine laboratory investigation including white cell blood count, haemoglobin, platelets, and biochemical tests were within normal values. Inflammation indices, ESR and CRP, were also normal. X-rays of the chest, abdomen, spinal cord and legs were normal. Electrocardiogram and abdominal ultrasound were also normal.

The patient complained for paresthesias and weakness in both legs. Neurologic examination revealed decreased muscle strength (3/5) to distal muscles of lower extremities without atrophies, loss of pinprick sensation to both feet and diminished sensation of light touch and deep pain. Proprioceptive sensation, position and vibration sense were also affected. Patellar reflexes were absent. Cranial nerves, cerebellar tests and ocular funduscopy examination were normal. There was a minor degree of decreased muscle strength (1/5) of the upper extremities.

Nerve conduction studies revealed decreased compound muscle axon potentials with relatively normal conduction velocities and absent sensory nerves action potentials at the lower extremities. Electromyography testing with concentric needle showed denervation potentials to the distal muscles of the lower extremities. Neurophysiology data was suggestive of a mixed sensorimotor axonal polyneuropathy with involvement of the lower extremities. Cerebrospinal fluid analysis revealed mildly elevated cell count (23 cells/ml) and elevated protein (473 mg/dl ; normal value : 10-45 mg/dl).

We supposed that the patient was suffering from acute axonal polyneuropathy complicating active distal UC. A total colonoscopy was performed, in order to evaluate the extent and the severity of the disease, which showed features of active colitis of moderate severity in the rectum (mucosal redness, oedema and friability with multiple erosions) and normal macroscopic appearance of sigmoid, descending and distal transverse colon. When we reached the proximal transverse colon, we noticed mucosal oedema, friability and spontaneous bleeding. Moreover, the lesions were worse in ascending colon and caecum, with the presence of frank mucosal ulceration. Terminal ileum had normal appearing mucosa macroscopically. Multiple biopsies were obtained from every part of the colon and terminal ileum in order to differentiate from Crohn's disease and to confirm the patchiness of the ulcerative colitis. Histological

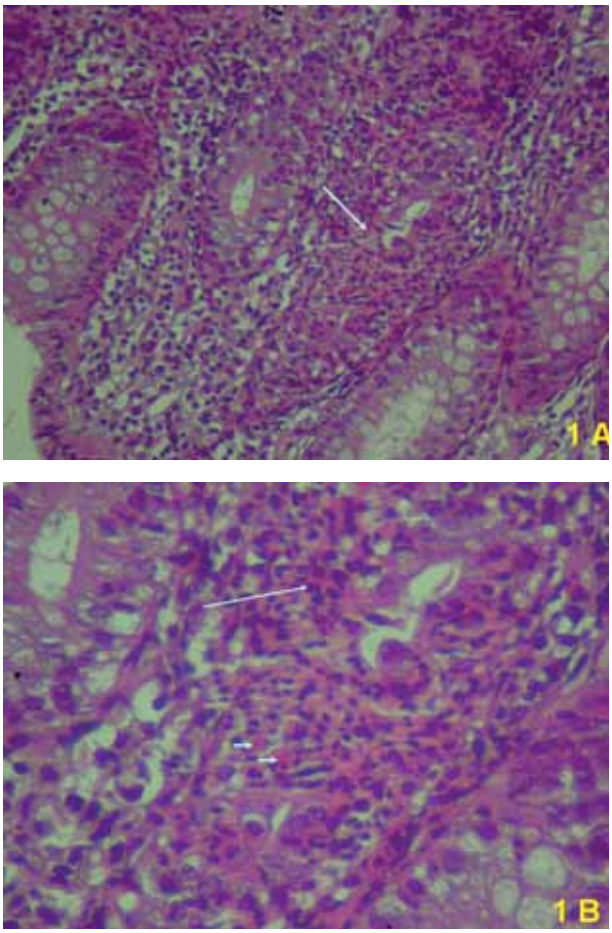

Fig. 1. — Histological findings in colonic biopsies. Chronic active ulcerative colitis with severe inflammation. (A) Dense infiltration of lamina propria with lymphocytes, plasmatocytes, and eosinophils leucocytes. Neutrophilic and eosinophilic infiltration of crypt epithelium (cryptitis) and crypt abscesses (arrow). There is also severe mucin depletion (magnification $\times$ 200). (B) Cryptitis with dense infiltration of neutrophils and eosinophils (long arrow) (magnification $\times$ 400).

examination of the biopsy samples showed features of chronic active ulcerative colitis with mucosal neutrophilic infiltration, plasma cell infiltration, crypt abscesses, depletion of goblet cells, crypt distortion and erosions (Figs. 1A & 1B) in proximal right and distal left colon separated by uninvolved sigmoid and descending colon.

Additional radiological and laboratory tests were performed in order to clarify the aetiology of polyneuropathy. Magnetic Resonance Imaging (MRI) examination of the brain and cervical spine were unremarkable. Laboratory tests including coagulation factors, immunoglobulins, thyroid function tests, Widal reaction, vitamin status and serology (including ANCA/ASCA) were normal, except for positive anti-ganglioside antibodies (anti-GM1). Cultures of blood and stool for bacteria, *Clostridium difficile*, *Campylobacter jejuni*, ova and parasites were negative.

Oral mesalamine tablets (3 g per day) were added to the treatment of active ulcerative colitis. Immunoglobulin (IVIg, 400 mg/kg) was administered intravenously for five consecutive days for the treatment of neuropathy and because of no response, 15 days later ; intravenous methyl-prednisolone (1 gr per day) was administered for five consecutive days, continued with oral prednisolone (20 mg/day). Neuropathic pain was treated with gabapentin titrated to 1800 mg per day. A slow parallel improvement of UC activity and polyneuropathy was noted during the next weeks. A very slow tapering of prednisolone over several months was started and azathioprine was added to the treatment (100 mg per day).

Colonoscopy, 2 months later, showed that ulcerative colitis was in remission with normal appearing mucosa throughout the colon and rectum. At the same time, the patient had almost completely clinically recovered from the polyneuropathy with absence of pain sensation and weakness of the legs. Tendon reflexes and muscle strength were normal.

Four months later, the patient was at the same clinical status, treated with oral mesalamine, azathioprine, and gabapentin. To date, three years later, the patient is on a steady clinical status with ulcerative colitis in remission and absence of neuropathy symptoms, treated with mesalamine (oral and rectal) and azathioprine.

Discussion

We presented a patient who developed acute motor and sensory polyneuropathy (AMSAN) during an exacerbation of ulcerative colitis.

Extraintestinal neurological complications associated with inflammatory bowel diseases (IBD) are well documented in the literature, albeit in a sporadic fashion (9,10). The exact overall incidence is unknown, as it may vary from 0.2% to 35.7% (10-14). Lossos *et al.* (10) reported that among 638 IBD patients (377 with CD and 261 with UC), 3% (10 CD and 9 UC patients) manifested neurological complications. Greenstein *et al.* (11) reported a small incidence (0.2%) of neurological complications among 700 patients with IBD. The differences of the incidence of neurological complications in IBD patients between these studies may be related to different disease definitions or to selection bias.

Acute cerebrovascular events like cerebral venous thrombosis (15), cerebral arterial occlusions (16), muscle disorders like dermatomyositis (17), myasthenia gravis and myositis (10), multiple sclerosis (18) and seizures (13) have been described. Peripheral polyneuropathy (PN) is one of the most frequently reported neurologic complications in both ulcerative colitis and Crohn's disease. It can be manifested as an acute inflammatory demyelinising polyneuropathy (AIDP or Guillain-Barré syndrome), as a chronic inflammatory demyelinising polyneuropathy (CIDP), or as a non-demyelinising sensory, motor or mixed sensory and motor axonal polyneuropathy or even as a single mononeuritis (10,13,19-23).

The pathogenesis of neurological complications in IBD is largely unknown, although coagulation abnormalities, vasculitis, factor V Leiden mutation, circulating immune complexes, autoimmunity, and an infective aetiology (e.g. *Campylobacter jejuni* infection causing an acute inflammatory demyelinising polyradiculoneuropathy) have been implicated (24-26). Polyneuropathy has been associated with vitamin B complex (B_1, B_6 and B_{12}) and folate deficiencies or with metronidazole neurotoxicity (27,28). In cases in which no specific etiological factor can be found, it has been suggested that a common autoimmune mechanism may be responsible for the polyneuropathy and IBD (27,29).

In the two large retrospective studies for neurological complications in IBD patients, the incidence of peripheral neuropathy (PN) was reported at 0.9% by Lossos *et al.* (10) and at 3.6% by Elsehety and Bertorini (14). In a recent retrospective study, Gondim *et al.* (30) presented the features of PN in 33 IBD patients (18 CD and 15 UC) and performed a systematic review of all case reports and series of IBD patients with PN. In their case series they found a male predominance, especially in non-demyelinising groups. In 33% of the CD patients and in 40% of the UC patients the neuropathy was related with active disease. In 67% of the CD patients and in 53% of the UC patients there were additional neurologic complications. Treatment options included immunosuppressive/immunomodulatory therapy (IVIg, intravenous or oral corticosteroids, azathioprine, cyclophosphamide, and etanercept), plasmapheresis and neuropathic pain management with non-immunomodulatory agents (gabapentin, antidepressants). Eleven out of 18 CD patients and 11 out of 15 UC patients had non-demyelinising PN. Seven out of 11 CD patients and 6 out of 11 UC patients with non-demyelinising PN, had axonal sensorimotor neuropathy. In the non-demyelinising UC subgroup, 51% had mild and 34% moderate improvement with immunomodulatory therapy. More specifically, the UC patients with axonal sensorimotor neuropathy showed variable responses with immunomodulatory therapy, from mild to good. The authors found in the literature, among other IBD patients with PN, 15 UC patients with sensorimotor involvement. The literature review shows that most IBD patients with PN (demyelinising or non-demyelinising) responded to immunomodulatory therapy.

The course of polyneuropathy may be parallel to the course of IBD, with an increased incidence during acute exacerbations (20,22,23) or may be independent, appearing even years before the symptoms from the gastrointestinal tract become evident (10,31,32). Larrode *et al.* (27), in a case series of 4 IBD patients, report that PN was associated with active inflammatory disease, but Gondim *et al.* (30), report an association with active disease in about one third of IBD patients. Moreover,

Lossos *et al.* (10) report in their case series that 4 out of 6 UC patients with PN had inactive disease.

Lossos *et al*. (10), report that PN was occurred predominately in UC patients, but Gondim *et al*. (30), report in their series and in the systematic review of the literature, an equal incidence of PN between UC and CD patients (not treated with metronidazole). In case series by Lossos *et al.* (10) most of UC patients with PN had additional extra-intestinal manifestations (5 out of 6). We did not find in the literature any data for association of severity and type of neuropathy with the extent of colitis.

Extraintestinal manifestations occur more commonly in patients with pancolitis (8). The mystery of the occurrence of such a rare neurologic manifestation in our patient who had ulcerative colitis limited to rectum was solved during performing total colonoscopy. When we reached the right colon we found out that the disease was more extensive than we had previously thought affecting the proximal right and distal left colon, with more severe findings in the proximal colon. Our practice is to perform total colonoscopy in all patients with ulcerative colitis, but this policy was delayed in this case. Another reason was that the flexible sigmoidoscopy was deceiving as we noticed a demarcation line of normal and inflamed mucosa at the rectosigmoid junction and the biopsies confirmed the diagnosis of distal ulcerative colitis. The treatment was appropriately decided to be topical as we could not imagine at that time the existence of the rare variety of ulcerative colitis with patchy distribution.

Traditional knowledge is that ulcerative colitis always involves the rectum and may extend to more proximal portions of the colon in a continuous fashion, without normal "skip areas". However, occasionally there are exceptions to this rule, with the presence of appendicular inflammation in patients with left sided ulcerative colitis (1), or with the presence of patchy inflammation or rectal sparing in treated or even in untreated UC patients (2-4,33). The exact incidence of proximal inflammation in patients with left sided ulcerative colitis (patchiness) is unknown, because endoscopic examinations for UC may be discontinued once the demarcation line between inflamed and normal colon is identified. Mutinga *et al.* (4), identified patchy right-sided colonic inflammation in 9.4% of a cohort of 127 UC patients who had left-sided disease, and in 3.4% of the entire cohort of 352 UC patients. There were no significant differences in clinical and demographic characteristics, including extraintestinal manifestations, between patients with patchy colitis and patients with confirmed left-sided colitis.

The presence of atypical patterns of inflammation, including rectal sparing and patchiness, in a subgroup of UC patients may be related to medical therapy, but there are studies that did not find such a correlation (2,3,34). Additionally, other studies found rectal sparing (relative or complete) in newly diagnosed untreated patients (35,36).

The presence of patchy inflammation involving other parts of the colon in a patient with previously diagnosed distal ulcerative colitis may have significant clinical implications as it could lead to a change of the diagnosis to Crohn's disease, or a change of the disease management (2). The diagnosis did not change in our patient as the histological findings were confirmatory for ulcerative colitis with absence of terminal ileum involvement and negative serology for ASCA and ANCA, but an explanation for the persistence of colitis and neuropathy symptoms was provided and a successful treatment modification for extensive colitis was set.

In our case, no etiological factor could be found for the acute peripheral neuropathy except for the flare of ulcerative colitis. To our knowledge, there is no previous report with acute peripheral neuropathy in ulcerative colitis with a patchy distribution. In the patient we described, all possible causes of acute polyneuropathy have been ruled out. MRI of the cervical spine along with clinical features excluded a diagnosis of myelopathy, since myelopathy has been reported as an extraintestinal complication in IBD (10). We did not identify any infectious, nutritional or metabolic cause. Medications such as metronidazole were not part of his treatment and haematological examinations ruled out the possibility of an underlying vasculitis. Furthermore, circulating immune complexes were excluded as a possible etiological factor because complement levels were within normal ranges. The patient had positive anti-ganglioside antibodies (anti-GM1), which are frequently found in polyneuropathy due to autoimmune disorders. The underlying disease was active UC which is proven to be associated with autoimmune disorders (37). Clinical improvement of colitis activity and neuropathy was noted with immunosuppressive therapy, but we cannot discriminate the role of the specific immunosuppressive therapy administered for the neuropathy and the role of the reduced of intestinal activity of the colitis in neurological improvement, since colitis and neuropathy shared a common therapeutic approach with corticosteroids and azathioprine. In previous case reports neurological improvement was noted after remission of ulcerative colitis treated with aminosalicylates and/or corticosteroids (32,38-40). All the above suggest that an autoimmune mechanism associated with ulcerative colitis might have assaulted the nervous system, in a not fully understandable way, and caused the neurologic complication in our patient.

In conclusion, the parallel course of the polyneuropathy and ulcerative colitis in our patient, allows us to assume that neurologic involvement was an immune-mediated extraintestinal manifestation associated with the activity, severity and course of ulcerative colitis.

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