Concurrent inflammatory bowel disease and gastrointestinal stromal tumor☆

Enfermedad inflamatoria intestinal concurrente con tumor del estroma gastrointestinal

There is evidence in the literature[1,2] of an association between intestinal adenocarcinomas and inflammatory bowel disease (IBD) from the first two cases of malignancy in patients with Crohn's disease described by Warren and Sommers in 1948 and Ginzburg et al. in 1956.[3,4] These cancers can particularly affect patients on treatment with immunosuppressants and most develop in segments where inflammation is present.[5]

Other primary intestinal cancers are rare in these patients, although cases of gastrointestinal lymphoma, carcinoid tumours, and a few cases of sarcoma have been reported in association with IBD. Gastrointestinal stromal tumours (GIST) are uncommon. They represent less than 3% of all gastrointestinal malignancies.[5,6] Most are found in the stomach (60%), followed by the jejunum and ileum (30%), duodenum (5%) and colon (5%).[5]

Our aim was to assess the possible concurrence of IBD and GIST in our hospital. We carried out a retrospective review of patients with histological study of GIST at the ''12 de Octubre'' University Hospital in Madrid from 1999 to September 2015. We searched these patients' electronic medical records, pathology reports and other clinical data from the cancer registry for concurrence of GIST and IBD.

In the period analysed, a total of 179 patients were diagnosed with GIST. In 16 patients (8.9%) there was no more data available in the medical records than the histological sample and the pathology report. Concurrence of IBD and GIST was found in two (1.2%) of the remaining 163 patients.

The first of these cases was an 82-year-old male with chronic obstructive pulmonary disease and Crohn's disease since 1996 with ileocecal involvement and inflammatory pattern (Montreal A3, L3, B1), diagnosed by endoscopic biopsy in the context of abdominal pain and anaemia. He took mesalazine 1 g/24 h as maintenance treatment. Subsequently he suffered several moderate-to-severe flare-ups in the form of upper gastrointestinal bleeding attributed to inflammatory activity (reclassification Montreal L3-L4) with good response to mesalazine 1 g/12 h and prednisone 30 mg/day, which were maintained after the flare-up as maintenance treatment, reducing the prednisone to 15 mg/day. In view of the rapid and effective response to steroids in each flare-up, immunosuppressive treatment was not proposed. In 2003, a new flare-up required a right hemicolectomy. During the surgical procedure, a localised jejunal GIST was diagnosed and completely resected. In retrospect, the lesion may have already been there when the patient was diagnosed with Crohn's disease, contributing to the initial clinical presentation, but not being visible in the initial diagnostic tests. In 2006 the patient suffered an episode of purulent peritonitis, which was attributed to either contained perforation or fistulisation of a bowel segment with active inflammation, given that no evidence of stromal tumour was found during surgery. On that occasion he required an ileostomy and splenectomy. He had no further flare-ups with the prior immunosuppression, but as a result of his age and comorbidity, the patient died from infectious respiratory complications in 2009.

The second case was a 45-year-old man with Crohn's disease in the ileum with a stricturing–penetrating pattern (Montreal A2, L1, B2-3) diagnosed in 1993 following abdominal pain and subacute obstruction symptoms. In 2001, he had a terminal ileum resection. From 2005 to 2011 he suffered three flare-ups with subacute obstruction symptoms which responded to corticosteroids (prednisone 0.5 mg/kg/day). After these episodes, the patient started maintenance treatment with mesalazine 1 g/12 h and azathioprine 100 mg/day, with no further flare-ups or new findings in routine colonoscopies until 2013, when he was diagnosed with advanced ileal GIST (liver and peritoneal metastases), which was found during follow-up of his underlying disease. Treatment with azathioprine was stopped and he was started on a first line of chemotherapy with imatinib 400 mg/day. In 2015, the dose was increased to 800 mg/day due to disease progression. A month later, the patient was admitted with bowel obstruction in relation to peritoneal metastases. Surgery was performed to re-establish transit with resection of the blocked ileal segment; it was not necessary to create a stoma. From then on, as progression of the disease was slow, it was decided to start treatment with sunitinib.

Cancer of the small intestine associated with Crohn's disease is almost exclusively adenocarcinoma or lymphoma.[1] GIST have rarely been described in relation to Crohn's.

Apart from the two described in our series, a review of the literature detected six further such cases in different articles.[5–7] Of these eight patients, seven were male and the average age was 40–50, except for two patients aged 81 and 82. In four of these patients the tumour was in the small intestine, in one it was in the gastric cavity, in another the pelvic cavity, in another liver metastases and peritoneal implants were found, and in the last patient, the location was not reported. The most common location reported in the literature is gastric (60%), but in the patients we reviewed, they were predominantly in the small intestine.

In four of these eight cases the tumour was in a segment affected by IBD. Only four of the reports state the length of time since onset of IBD when they were diagnosed with the stromal tumour.

One of the cases was an ulcerative colitis diagnosed 13 years earlier. The patient required a total colectomy for disease refractory to immunosuppressive therapy, including biological and corticosteroid-dependent drugs. After the colectomy, he was found to have upper gastrointestinal bleeding related to the gastric GIST, which was resected.

Another patient had been diagnosed with Crohn's disease one year previously and, during a laparotomy because of dull abdominal pain and image compatible with intussusception, a GIST was found in the small intestine in a segment with an inflammatory pattern.

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Another patient had been diagnosed with Crohn's disease seven years earlier, and a jejunal GIST was found incidentally in a non-inflamed segment during a right hemicolectomy for a flare-up. The patient had been on treatment since diagnosis with mesalazine and prednisone 15 mg/day.

The last of the cases had been diagnosed with Crohn's disease ten years prior to the finding of disseminated GIST with liver and peritoneal metastases. He had been on maintenance treatment with mesalazine 1 g/12 h and azathioprine 100 mg/day since diagnosis.

In three of them, the GIST was diagnosed concurrently with the IBD.[1]

The majority of patients with small bowel tumours associated with Crohn's disease have a long history of IBD prior to developing a malignancy. The concurrence of the two diseases in three patients and the low prevalence of sarcomas in our series (1.2%; 2 out of 163 patients) suggest a pure coincidence of two distinct disease processes rather than a potential causal relationship. The correlation between GIST and IBD is subject to debate. There is currently no evidence to support any association.[5] The fact that patients with IBD undergo more diagnostic procedures, advances in these procedures and the fact that these patients are surviving for longer all increase the likelihood of finding stromal tumours that would otherwise go unnoticed.

However, since these diseases can cause similar symptoms, bowel cancer (especially types located in the small intestine) should be considered in patients whose symptoms are not resolved with IBD treatment.

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María Agud Fernández[a,*], Flora López López[b], Carmen Díaz Pedroche[a], Carlos Gómez-Martín[b]

[a] *Servicio de Medicina Interna, Hospital Universitario 12 de Octubre, Madrid, Spain*
[b] *Servicio de Oncología Médica, Hospital Universitario 12 de Octubre, Madrid, Spain*

* Corresponding author.
E-mail address: mariaagud@gmail.com
(M. Agud Fernández).

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Autoimmune Hepatitis (Immune-Mediated Liver Injury) Induced By Rosuvastatin

Hepatitis autoinmune (lesión de hígado mediante la inmunidad) inducida por rosuvastatin

To the Editor:

Autoimmune hepatitis induced by drugs represents an increasingly known category of hepatotoxicity due to medication .[1,2] This liver disorder is also known as drug induced autoimmune like hepatitis or autoinmune-like drug-induced liver injury. Some of the drugs associated with this pathology include nitrofurantoin, minocycline, diclofenac, anti-TNF-α, α-methyl DOPA and statins .[1,2] We present a case report of a patient treated with rosuvastatin who showed liver injury with autoimmune features.

A 47 year-old white man with history of ischemic cardiopathy and hyperlipoproteinemia, with previous normal liver enzyme values, came to our outpatient clinic due to hypertransaminasemia. The patient denied any history of autoinmune disorders, liver diseases, alcohol or herbs use. Eleven months earlier he had started treatment with Rosuvastatin (he had switched from Atorvastatin). He was also receiving aspirin 100 mg and Bisoprolol 2.5 mg. Ten months after starting treatment with Rosuvastatin revealed a serum alanine aminotransferase (ALT) of 201 U/L (n: 0-41 U/L) and aspartate aminotransferse (AST) of 112 U/L (n: 0-37) (Table 1). The patient showed no symptoms and Rosuvastatin was discontinued. About 2 weeks after stopping therapy with Rosuvastatin, aspartate animotransferase and alanine aminotransferase levels continued to increase (AST 151 U/L, ALT 266 U/L). Serological testing for hepatitis A, B and C were negative, as were testing for Epstein-Barr virus and cytomegalovirus. Antinuclear antibodies were present (160); test for antismooth muscle antibodies, antimitochondrials and anti-LKM were negative and IgG was normal. Liver ultrasound examination was normal too. A study for leucocyte antigen revealed HLA-DRB1 *11:04 and *15:01; DR3 and DR4 were absent. Autoimmune Hepatitis (AIH) international score was 11(probable), CIOMS/RUCAM Score was 5 (possible) and AIH-drug induced liver injury (DILI) was presumed. A month after discontinuing the drug, the ALT-AST