Chronic diarrhea and deep vein thrombosis during treatment with olmesartan

Diarrea crónica y trombosis venosa profunda durante el tratamiento con olmesartán

Chronic diarrhea is one of the most challenging entities in gastroenterology. Since 2012, olmesartan has been recognized as a causal agent for chronic diarrhea that should be included in the differential diagnosis of patients with villous atrophy and negative celiac serologies.

A 69-year-old woman was taken to the emergency room with a progressive decrease in her level of consciousness, together with lower limb edema. The patient’s relatives stated that 6 weeks earlier she began to experience progressive, large-volume, watery stools (5-6 episodes/day), without blood or abdominal pain. Because of anorexia and weight loss (± 2 kg), the patient was previously evaluated by her general practitioner and was empirically medicated with metronidazole and ciprofloxacin plus a probiotic, without improvement. A colonoscopy was also performed that identified no macroscopic abnormalities (no biopsies were done). Her past medical history of interest included high blood pressure treated with olmesartan and aliskiren and gastroesophageal reflux disease treated with pantoprazole. The patient had been taking these medications for approximately one year. There were no relevant epidemiologic contacts.

Upon physical examination, she had 8 points on the Glasgow Coma Scale and presented with tachypnea and hemodynamic instability. Her mucosae were dehydrated and her abdomen was not painful. Bilateral edema was more pronounced on the left side. Proctologic examination identified no abnormalities.

The initial blood test results were: Hb: 14.5 g/l; WBC: 14.7×10⁹/l; N: 87.9%; platelets: 213×10⁹/l; Na: 153 mmol/l; K: 2.7 mmol/l; BUN: 77 mg/dl; creatinine: 3.9 mg/dl; CRP: 16 mg/l; INR: 1.5; albumin: 2.5 g/dl. Arterial blood gas showed metabolic acidosis (pH: 7.247; HCO3: 5.3 mEq/l).

Subsequent ultrasound of the lower limb revealed extensive deep vein thrombosis (DVT) involving the femoral and left popliteal vein. Intravenous anticoagulation was begun.

Kidney function improved, and so a CT scan was performed (fig. 1) that confirmed the extension of the DVT. No other anomalies were observed. Given the characteristics of the diarrhea, an upper endoscopy was done, showing no macroscopic abnormalities (biopsies were taken).

Microbiologic evaluation of stools and Clostridium difficile toxin assay were negative. Subsequent blood tests reported iron deficiency (iron: 28 ug/dl; ferritin: 56 ng/ml; transferrin: 85 mg/dl), a low folate value (2.0 ng/ml), and a total cholesterol level of 103 mg/dl. HIV screening was also negative. Serum immunoglobulins, fibrinogen, aminotransferases, vitamin B12, TSH, FT4, calcium, magnesium, phosphorus, and anti-TG were normal.

The histologic examination (fig. 2) showed subtotal villous atrophy with lymphocytic infiltration in the lamina propria. The prothrombotic factor study was negative.

The most common cause of villous atrophy is celiac disease. Nevertheless, when dealing with a negative celiac serology other diagnoses should be considered, such as Crohn’s disease, enteric infections, collagenous/tropical sprue, common variable immunodeficiency, autoimmune enteropathy, hematologic malignancies, and drug-induced enteropathy.

After ruling out other possible causes, we established the diagnosis of olmesartan-induced enteropathy.

Improvement was rapid with the suspension of olmesartan, and 9 days after admission, the patient had solid, shaped stools with one bowel movement a day. Olmesartan was substituted by hydrochlorothiazide and the patient was discharged with oral iron therapy, folic acid supplementation, and apixaban. Re-exposure to pantoprazole and aliskiren did not condition symptom reappearance.

Two months later, blood tests confirmed the patient’s good progression. Subsequent endoscopy and colonoscopy showed no macroscopic or histologic abnormalities.

Olmesartan is an angiotensin II receptor blocker (ARB) used for treating high blood pressure since 2002. The first report of olmesartan-induced enteropathy was in 2012 and since then, a vast number of case reports and reviews have been published describing this adverse event. Olmesartan-induced diarrhea pathogenesis is still unclear. However, the long interval between olmesartan therapy commencement and the development of symptoms suggests a cell-mediated immune mechanism.

Whether it is a class effect is still doubtful, given that there are reports describing similar effects in patients taking other ARBs, even though those events appear to be less frequent.

Its clinical spectrum is vast, but the majority of patients experience diarrhea, weight loss, and fatigue. One interesting finding in our case was the DVT episode. DVT is a rare side effect of olmesartan, and to the best of our knowledge, there are no reports in the literature correlating olmesartan-induced enteropathy with DVT. The most plausible explanation could be the prothrombotic state secondary to dehydration and patient immobility.

Normocytic normochromic anemia and hypoalbuminemia are the most frequent laboratory abnormalities at presentation. Upper endoscopy may be normal, or show a nodular appearance of the duodenal mucosa. The most common histopathologic finding is flattening of the duodenal villous pattern (either total or partial) and increased duodenal intraepithelial lymphocytes (IELs). Contrary to celiac disease, flattening of the duodenal villous pattern is not always associated with IELs.

Regarding treatment, literature reports have demonstrated that withdrawal of olmesartan conditioned clinical remission in all patients and histologic duodenal recovery in most of them.

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Figure 1  CT scan revealing an extensive DVT involving the femoral and left popliteal vein.

Figure 2  Biopsies of the small intestine showing villous atrophy and chronic lymphocytic infiltration of the lamina propria (hematoxylin and eosin x15).

Our case is a typical example of the lack of awareness of this new entity by physicians. Because of the late diagnosis, the clinical course was continued and conditioned a catastrophic clinical set of events that included severe dehydration, hypovolemic shock, acute kidney insufficiency, metabolic acidosis, and DVT.

Conflict of interest

The authors declare that there is no conflict of interest.

References

Bowel obstruction involving capsule endoscopy in a patient with Peutz-Jeghers syndrome\textsuperscript{a,4,5}

Obstrucción intestinal por cápsula endoscópica en un paciente con síndrome de Peutz-Jeghers

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited disorder characterized by hamartomatous polyps and mucocutaneous pigmentation, and its prevalence is 1 out of every 8,300 to 29,000 live births. The most frequently affected areas of the gastrointestinal tract are the small bowel, jejunum, and ileum (65-95%), and to a lesser degree, the colon (60%) and stomach (50%). The disease can give rise to complications such as intestinal lumen obstruction, bleeding, and a greater risk for intestinal and extra-intestinal neoplasias.\textsuperscript{1-3}

A 30-year-old man was seen at the Instituto de Investigaciones Médico-Biológicas of the Universidad Veracruzana. The patient’s family history included a father with intestinal polyps. He presented with a one-year progression of symptoms of abdominal pain, nausea, bloating, and constipation, accompanied with anorexia, adynamia, and weight loss. A relevant sign was the presence of hyperchromic spots on the upper lip and palate. Colonoscopy revealed numerous sessile polypoid lesions that varied in size from 0.3 to 2 cm throughout the entire colon and in the terminal ileum. The histopathologic study reported pedunculated hamartomatous polyps with a stromal and epithelial histologic component and an arborescent proliferation of smooth muscle, resulting in the diagnosis of PJS.

One year later, the patient returned complaining of persistent pain, now located at the left flank, abdominal bloating, important constipation, nausea and vomiting, and general malaise. A Pillcam (Given Imaging) capsule endoscopy was performed that showed numerous sessile polyps in the gastric chamber, duodenum, jejunum, and ileum. Passage to the colon was not possible due to the presence of a large polyp. In the following 7 days, the pain intensified and was accompanied with signs and symptoms of marked bowel obstruction, with no expulsion of the video capsule. The symptoms were corroborated through a plain abdominal film that showed the capsule located in the ileum. An antegrade double-balloon enteroscopy was then carried out, through which numerous bleeding ulcerated, eroded, and branched polyps were visualized, along with the video capsule that was lodged in the ileum. A large polyp did not allow the endoscope to pass, corroborating the bowel obstruction (fig. 1A). The maneuvers to extract the capsule were unsuccessful due to its impact on the stenosed site, and so the patient underwent surgical resection of a 77-cm segment of the terminal ileum with anastomosis of the ileum to the transverse colon (fig. 1B).

The histopathologic study of the specimen showed countess polyps measuring from 0.2 to 5 cm in size. The largest one obstructed 90% of the lumen and the capsule was found in the proximal part of the lesion. Microscopic study revealed multiple ulcerated and bleeding polyps, and the stenosed lesion corresponded to a focal polyp with high-grade dysplasia and a stromal pseudo-invasive aspect (fig. 2A and B).

After bowel resection, the patient presented with ischemic stroke in the right hemisphere associated with a

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\textsuperscript{a} Please cite this article as: Roesch-Dietl Fan, Cano-Contreras AD, Meixueiro-Daza A, Remes-Troche JM, Grube-Pagola P. Obstrucción intestinal por cápsula endoscópica en un paciente con síndrome de Peutz-Jeghers. Revista de Gastroenterología de México. 2018;83:202–204.