biliary-cysts communication, adding complementary diagnostic information to conventional MR sequences and allowing a conclusive diagnosis of CD in the appropriate clinical setting, without the use of invasive methods (e.g., endoscopic retrograde cholangiography and percutaneous transhepatic cholangiography), which may be associated with complications such as bleeding, infection and pancreatitis.[4]

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Lee NK, Kim S, Lee JW, Lee SH, Kang DH, Kim GH, et al. Biliary MR imaging with Gd-EOB-DTPA and its clinical applications. Radiographics. 2009;29:1707–24.
2. Santiago I, Loureiro R, Curvo-Semedo L, Marques C, Tardáguila F, Matos C, et al. Congenital cystic lesions of the biliary tree. Am J Roentgenol. 2012;198:825–35.
3. Ahmadi T, Itai Y, Minami M. Central dot sign in entities other than Caroli disease. Radiat Med. 1997;15:381–4.
4. Fulcher AS. CT cholangiography: advantages and disadvantages compared with MR cholangiography in the evaluation of the biliary tract following liver transplantation. Liver Transpl. 2004;10:1071–2.

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Poor correlation between acute phase reactants and intestinal involvement in patients with onset of Crohn's disease under treatment with an interleukin-6 inhibitor due to seronegative arthropathy☆

Mala correlación entre reactantes de fase aguda y afectación intestinal en paciente con comienzo de la enfermedad de Crohn bajo tratamiento con inhibidor de IL-6 por artropatía seronegativa

This case concerned a 44-year-old woman, with no drug allergies or history of tobacco, alcohol or illicit drug use, with seronegative arthritis that commenced at age 18 in the form of asymmetric oligoarthritis, predominantly in the large joints. At age 22, she began to suffer rapidly destructive right coxitis, which required right hip replacement (RHR) at age 42. Rheumatoid factor, anti-citrullinated peptide antibodies, antinuclear antibodies and HLA-B27 tests were negative. She continued with remission induction therapy with hydroxychloroquine, gold salts (discontinued due to inefficacy) and methotrexate (MTX) (discontinued due to intolerance). In 2006, she initiated treatment with adalimumab (discontinued at 3 months due to skin rash) and then with etanercept (2008–2009), with partial response, and required glucocorticoids during the arthritis flares. She then received rituximab every 6 months (2009–2011, interrupted for the RHR surgery). She required infiltration of the right carpus for a new arthritis flare, and recommenced rituximab in June 2014, with a partial response.

In July 2014, the biological treatment was switched after the patient began to lose weight and became anaemic, with deterioration in her general health and arthritis, and elevated acute phase reactants (erythrocyte sedimentation rate [ESR] 64 mm/h and C-reactive protein [CRP] 56 mg/L (normal value: <5 mg/L). As a result of the marked systemic component, intravenous tocilizumab (TCZ) monthly monotherapy (due to intolerance to MTX) was initiated in October 2014.

In January 2015, she was admitted to the gastroenterology department for loose stools (5–7 day) with no blood, pus or mucus, abdominal pain and 10-kg weight loss, which had commenced 1 month previously. Physical examination was remarkable for abdominal pain predominantly in the left flank, with no palpable masses or visceromegaly. Laboratory tests showed neither leukocytosis nor anaemia (haemoglobin 14.2 g/dL), with CRP 0.24 mg/L and albumin 44 g/L. To complete the study, she underwent fibrogastroscopy, which was normal, and colonoscopy, which showed extensive, deep ulcers with healthy interlesional mucosa extending from 12 cm from the anal margin to the caecum, as well as the terminal ileum; 15 cm were affected with minute aphthae (Fig. 1). Histopathology findings were consistent with inflammatory bowel disease (IBD). She later presented high faecal calprotectin (FC) levels of 2714 mg/kg faeces (normal value <100 mg/kg). This was diagnosed as a severe flare-up of ileocolic Crohn disease (CD), with associated

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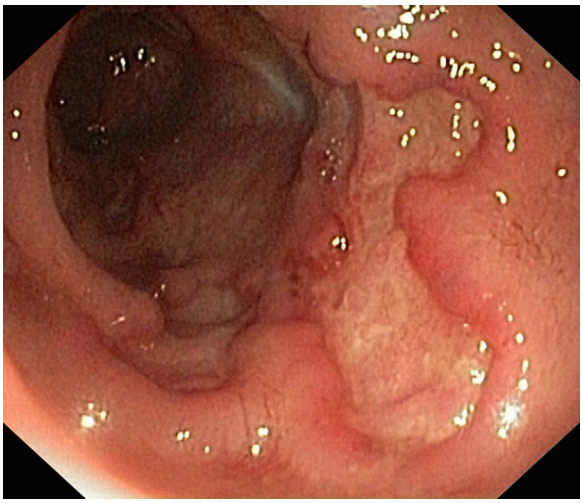

Figure 1 Extensive, deep ulcers with healthy interlesional mucosa along the entire length the colon.

peripheral arthropathy. The patient started treatment with full-dose corticosteroid therapy (40 mg/day), azathioprine 150 mg/day and total enteral nutrition (TEN). She progressed well, with a decrease in the daily number of stools, as well as resolution of the abdominal and joint pain, and was discharged home.

We consider this clinical case to be of particular interest, firstly because of the sequence of clinical presentation, with erosive peripheral arthropathy 20 years before the intestinal manifestation of CD, a situation that accounts for only 10% of cases. Secondly, the normality of the biological parameters is remarkable, despite having significant mucosal involvement on the colonoscopy. Numerous cases of severe infections with normal biological reactants have been described in patients with rheumatoid arthritis on treatment with TCZ, but none in patients with CD and normal biological reactants in the context of anti-interleukin-6 (anti-IL-6) therapy.[1–4]

Joint symptoms are the most common extra-intestinal manifestation of CD (10–35%), either in the form of axial spondylarthropathy (sacroilitis and spondylitis) or peripheral arthritis, acute or chronic. Peripheral arthritis is usually related with the IBD activity, and generally appears simultaneously with IBD flares. Involvement is often pauciarticular, asymmetric, transient and self-limiting, although there are forms with persistent chronic activity, as in the case described. Although these manifestations respond to IBD treatment, it is often necessary to add remission induction drugs or administer local glucocorticoid injections.[5]

The normality of the biological reactants, despite the major ileocolic involvement as a result of CD, could be explained by the effect of the anti-IL-6 therapy. Interleukin 6 is a pro-inflammatory cytokine produced by various cell types, including monocytes, lymphocytes and fibroblasts, which participate in multiple biological processes such as formation of acute phase proteins and hepcidine in the liver, increased megakaryocyte levels with systemic thrombocytosis, differentiation of osteoclasts and consequently osteoporosis, and activation of macrophages, B- and T-cells, which cause chronic inflammation. All these pro-inflammatory actions link it to the pathophysiology of many autoimmune inflammatory diseases, such as CD.

TCZ is a humanised monoclonal antibody that targets both the soluble and membrane-bound forms of the interleukin-6 receptor. It has been approved in Europe as monotherapy or in combination with MTX for the treatment of adults with moderate-severe rheumatoid arthritis who respond inadequately to, or are intolerant to, one or more disease-modifying anti-rheumatic drugs or anti-tumour necrosis factor-alpha agents.[6] However, it is not effective for CD, as interleukin-6 does not appear to be directly implicated in the pathophysiological mechanism of this disease. In fact, the results of different studies in patients with IBD treated with TCZ have shown a clinical response in more than 50% of cases, but no endoscopic or histological remission when compared with the placebo group.[7–9]

In this case, a simple, useful tool to clarify the diagnosis is FC. Calprotectin is an antimicrobial protein that accounts for 60% of the cytosolic proteins in granulocytes; its presence in stool is directly proportional to neutrophil activity in the intestinal lumen.

FC has been proposed as a biomarker of intestinal inflammation, as it correlates better with the degree of inflammation than serological markers and clinical indices, and has a sensitivity for detecting mucosal activity that varies from 70% to 100% and a specificity of 44–100%, according to the cut-off point in used in different studies.[10]

In conclusion, normal biological reactant levels cannot rule out IBD in a patient with clinical suspicion of the disease. In this case, FC seems to be an excellent diagnostic test to select those patients requiring further study.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Hirao M, Nampei A, Shi K, Yoshikawa H, Nishimoto N, Hashimoto J. Diagnostic features of mild cellulitis phlegmon in patients with rheumatoid arthritis treated with tocilizumab: a report of two cases. Mod Rheumatol. 2011;21:673–7.
2. Makino T, Kaito T, Tsuboi H, Fujiwara H, Yonenobu K. Late-onset deep surgical-site infection after posterior lumbar interbody fusion in a patient treated with tocilizumab; unusual changes in inflammatory markers. Eur Spine J. 2014;23 Suppl. 2: S296–301.
3. Bari SF, Khan A, Lawson T. C reactive protein may not be reliable as a marker of severe bacterial infection in patients receiving tocilizumab. BMJ Case Rep. 2013;October, pii:bcr2013010423.
4. Ljung L, Smeds J, Persson G, Jirlén L, Toolanen G. Immunosuppression may mask severe infection. Septic arthritis in tocilizumab treatment yielded only modest acute-phase reaction [Article in Swedish]. Lakartidningen. 2012;109: 1678–9.
5. Domènech E, Mañosa M, Cabré E. Manifestacions extraintestinals a la malaltia inflamatòria intestinal. Suplements dels Ann Med. 2014;97 Suppl. 1:S1–20.
6. Rueda J, Blanco R. Tocilizumab en artritis reumatoide. Reumatol Clin. 2011;6 Suppl. 3:29–32.
7. Ito H, Takazoe M, Fukuda Y, Hibi T, Kusugami K, Andoh A, et al. A pilot randomized trial of a human anti-interleukin-6 receptor

monoclonal antibody in active Crohn's disease. J Gastroenterol. 2004;126:989–96.
8. Ito H. Treatment of Crohn's disease with anti-IL-6 receptor antibody. J Gastroenterol. 2005;40 Suppl. 16:S32–4.
9. Ito H. Novel therapy for Crohn's disease targeting IL-6 signalling. Expert Opin Ther Targets. 2004;8:287–94.
10. Rodríguez F. Calprotectina fecal en el diagnóstico de enfermedades inflamatorias. Gastroenterol Hepatol. 2013;36:400–6.

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Pneumatosis intestinalis due to 5-fluorouracil chemotherapy☆

Neumatosis intestinal secundaria a quimioterapia con 5-fluorouracilo

Pneumatosis intestinalis (PI) is the presence of gas in the intestinal wall. It has multiple aetiologies, many of them benign but others with high mortality.[1–4] Its location and radiological characteristics are indicative, but non-specific, and not pathognomonic for differentiating benign from life-threatening PI[2,3]; treatment and prognosis depend on the identified cause.

Establishing the cause of PI can be complex in patients with cancer, especially if there is a history of previous surgery, intra-abdominal stents, immunosuppression and chemotherapy.[1] Several chemotherapy agents, including 5-fluorouracil (5-FU) have been associated with the development of PI,[5–7] both in monotherapy and in combined regimens.

In addition to its indication as a first-line treatment in various solid tumours, 5-FU is also used with palliative intent in gastrointestinal and head and neck tumours.

We present the case of a patient with metastatic adenocarcinoma of the gastro-oesophageal junction on palliative chemotherapy with 5-FU, who presented secondary intestinal toxicity in the form of PI. We review the clinical and radiological characteristics of the condition, as well as its aetiopathogenesis and treatment.

The case concerns a 65-year-old man with gastrostomy tube and a history of stage IV adenocarcinoma of the gastro-oesophageal junction (lung metastases) who was receiving palliative chemotherapy with a cisplatin (70 mg/m^2) and 5-FU (3000 mg/m^2) regimen every 21 days. After the fourth cycle of treatment, he presented to the emergency department for abdominal distension, colicky pain and diarrhoea (6 stools/day) with no mucus, blood or pus, which had commenced 4 days after completion of the 5-FU infusion. He was afebrile, and physical examination found: distended, non-tender abdomen with abundant bowel sounds and no signs of peritoneal irritation. Laboratory tests showed hypernatraemia, with sodium 148 mEq/L, and hypokalaemia, with potassium 2.5 mEq/L, with no evidence of sepsis or cytopenias. Radiological findings on the abdominal X-ray and computed tomography (CT) scan are described in Fig. 1.

A tentative diagnosis of PI probably secondary to 5-FU treatment was made, and the patient was admitted for intravenous fluid replacement, bowel rest and oxygen therapy 2 L/min. He remained afebrile, with gradual improvement in the abdominal distension and diarrhoea and no signs of peritoneal irritation. Blood and stool cultures were negative. After 10 days of treatment, abdominal CT showed a significant decrease in the pneumo- and retropneumoperitoneum.

PI was first described in 1908,[8] but has since been known by various names, and several possible causes have been reported.[1–7]

Although PI is probably a multifactorial condition, the bacterial and mechanical pathogenesis theories are the most widely accepted. The bacterial theory suggests that the gas-forming bacilli that colonise the intestine enter the mucosa due to increased mucosal permeability or disruption of the bowel wall, introducing gas into the wall. According to the mechanical theory, the presence of continuity solutions in the intestinal mucosa allows gas to enter the bowel wall, especially if there is an increase in the intraluminal pressure.[9,10] In murine models, the cytotoxic effect of 5-FU on the cells of the intestinal mucosa reduces proliferation and increases cell apoptosis in the intestinal crypts; it also affects immunocompetent cells, enabling bacterial translocation from the lumen into the bowel walls and even into the bloodstream.[10]

PI is a radiological sign and not a diagnosis in itself, and its radiological characteristics are indicative but not pathognomonic for differentiating between benign conditions and potentially serious diseases.[1–4,8] This distinction can be especially complex in patients with cancer who, as mentioned, may have received treatments that have been associated with the development of PI. Pear[1] classified some causes of PI according to their prognosis (Table 1).

The absence of warning signs such as fever, signs of peritoneal irritation and laboratory findings of cytopenia and/or sepsis are probably the most important factors when assessing the possible causes and treatment of a patient with PI. Mimatsu et al.[7] reported a case of 5-FU treatment-related PI that was symptomatically and radio-

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