CLINICAL CASE

PULMONARY GRANULOMATOSIS IN ULCERATIVE COLITIS, AN UNCOMMON EXTRAINTESTINAL MANIFESTATION

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Abstract

This is an ex-smoker patient with a history of long-standing ulcerative colitis with persistent activity and refractory to several biological therapies. She has ongoing symptoms, such as bloody diarrhea, weight loss, and severe anemia that require regular intravenous iron transfusions. Despite attempts to control the disease with different medications, including Infliximab and Vedolizumab, the patient remains symptomatic and elevates markers of disease activity, such as fecal calprotectin.

At follow-up, the patient presented with a chronic cough, which led to studies that revealed the presence of a hypermetabolic pulmonary nodule in the left lower lobe, suspected of primary pulmonary neoplasia, and an atypical pulmonary resection was performed.

Diagnosis reveals possible respiratory granulomatous intestinal epithelial metaplasia due to histological findings in the lung, consistent with an uncommon extraintestinal manifestation in the context of uncontrolled ulcerative colitis.

Finally, a change of therapeutic target with Ustekinumab was initiated due to the previous failure of anti-TNF and Vedolizumab treatments in the control of ulcerative colitis, with clinical improvement in the digestive and respiratory spheres.

Keywords: ulcerative colitis, granulomas, chronic cough.

Introduction

Inflammatory Bowel Disease (IBD) is characterised by chronic recurrent intestinal inflammation. There are two well-defined entities: Crohn's Disease (CD) and Ulcerative Colitis (UC). While CD causes discontinuous transmural inflammation in any section of the digestive tract and may be

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associated with fistulas, abscesses or strictures, UC causes a continuous alteration of the ultrastructure of the colon.

In clinical terms, persistent abdominal pain, weight loss, asthenia, fever or feverishness or diarrhoea with pathological products are the most frequent symptoms at the onset of IBD, the intensity of which correlates with greater severity[1].

Other clinical manifestations associated with IBD are extraintestinal manifestations (EIMs). The prevalence of EIMs ranges from 6% to 47%, affecting more women (50%) than men (34%)[2]. However, in a not insignificant proportion of cases (25.8%), EIMs appear before formal diagnosis of IBD, with a diagnostic delay of up to 5 months and as long as 2 years[3].

EIMs can affect any system or apparatus[4], with musculoskeletal manifestations (peripheral arthritis type 1 or 2 and HLA B27 axial spondyloarthropathy), cutaneous (erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, psoriasis and Sweet's syndrome), ophthalmological (episcleritis, scleritis and uveitis), hepatobiliary (primary sclerosing cholangitis), renal and pulmonary, the latter being more rare.

Infrequent EIMs include those affecting the pulmonary sphere. It is essential to recognise the common presenting pulmonary symptoms (dyspnoea, wheezing, dry or productive cough, pleuritic pain, fever or stridor). However, between 37% and 55% of patients with IBD may present with abnormalities on pulmonary function tests, chest imaging or histopathology in the absence of respiratory symptoms[5].

Pulmonary EIMs is very diverse and can affect the airways (granulomatous or obliterative bronchiolitis, bronchiectasis, chronic bronchitis), the parenchyma (organised interstitial, lymphocytic or eosinophilic pneumonia and granulomatous interstitial lung disease) or diffusely (interstitial pneumonitis, abscesses, granulomas)[6].

The prevalence of pulmonary EIMS is not clearly defined in the literature, with a low prevalence found among adolescents, a group in which IBD is very common[7]. A greater association with CD has been seen, although they may appear independently of IBD activity, which makes their suspicion and management even more difficult.

Early detection of EIMs is of vital importance, as it affects the overall management of IBD patients[8]. On the one hand, IBD increases the overall burden of disease, leading to increased morbidity, reduced quality of life and the development of complications. In addition, such detection requires a multidisciplinary approach involving a range of specialists to achieve optimal management of intestinal and extraintestinal pathology. Patient education and support is also important to control modifiable environmental factors and ensure adherence to treatment.

A fundamental pillar is the medical treatment of IBD9. There are currently several therapeutic steps ranging from topical treatments (suppositories, enemas or Mesalazine foams) to oral treatment (mesalazine, beclomethasone, budesonide or prednisone). If clinical, analytical or endoscopic remission is not achieved, it is necessary to resort to biological therapies and small molecules, with a proven efficacy and safety profile in routine clinical practice. This allows better control of IBD, as well as those EIMs that are parallel and dependent on digestive activity (peripheral arthritis type 1, erythema nodosum, aphthous stomatitis or episcleritis, among others).

We present the clinical case of a patient with uncontrolled UC refractory to conventional treatment and various biological lines who, during close follow-up in the clinic, presented with a chronic cough attributable to pulmonary granulomatosis, a rare pulmonary EIM.

Clinical case

The patient is a 22-year-old former smoker of (half a pack a day), with no medical history of interest in the digestive sphere, who was diagnosed in 1998 with UC. Since then, the patient has presented a variegated clinical course that has required the administration and substitution of multiple treatments: Oral and topical mesalazine, beclomethasone, continuous rounds of oral corticosteroids up to mercaptopurine, which was substituted to infliximab due to lack of improvement, initiated after performing the prebiological study which ruled out contraindications (Among them, the presence of latent tuberculosis). Despite maximum intensification of infliximab, remission of the disease was not achieved either, changing the therapeutic target to vedolizumab, with the same clinical, analytical and endoscopic results despite maximum intensification. This led the patient to continually visit the emergency department, with multiple hospitalisations since the onset of the disease.

Even with all the therapeutic adjustments described, the patient has presented multiple outbreaks over the years, with persistent symptoms such as severe bloody diarrhoea (more than 8 bowel movements per day), significant weight loss (10 kg), faecal incontinence and severe anaemia that has required periodic intravenous iron transfusions. In addition, he has suffered on 2 occasions from infectious colitis secondary

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to *Clostridium Difficile*, which responded adequately to vancomycin.

From the analytical point of view, the difficulty in controlling the disease translates into a persistent and not very fluctuating elevation of acute phase reactants: faecal calprotectin around 2000-4000 IU/L, anaemia (haemoglobin around 10 mg/dL), hypoalbuminaemia and thrombocytosis. All this indicates a high inflammatory burden of UC, which requires endoscopic controls in the face of continuous changes in treatment, with findings of diffuse UC with mild-moderate activity in the last colonoscopy performed in 2024.

During close follow-up in the gastroenterology department, the patient began with a productive brown phlegm cough of 2 months' duration that did not improve with inhalation treatment or antibiotic therapy. Additional tests included negative sputum cultures, negative Mantoux and IGRA, normal respiratory function tests and a chest CT scan showing two nodular images in the right lower lobe (RIL) and another in the left lower lobe (LIL) of approximately 12 mm with indeterminate characteristics (Figure 1).

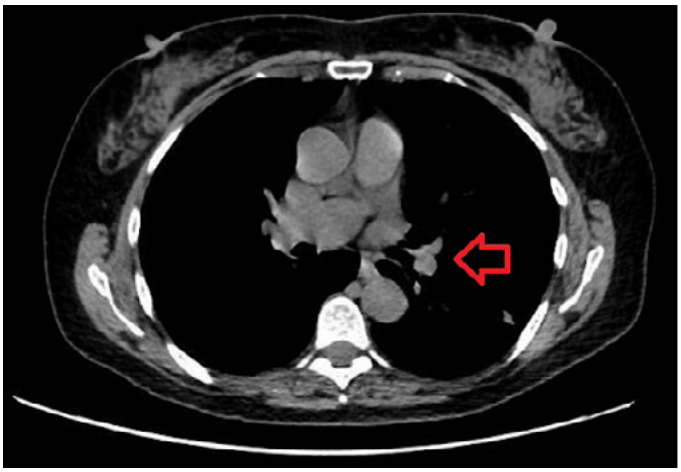

Figure 1. ***Cross-sectional CT scan of the chest showing a nodular image in LIL of about 12 mm of undetermined characteristics (red arrow).***

Positron Emission Tomography (PET-CT) was performed and showed a hypermetabolic pulmonary nodule in LIL (Figure 2). Heterogeneous intestinal metabolic activity with hypermetabolic mesenteric and retroperitoneal adenopathies was also identified, and a multidisciplinary assessment was recommended for suspected primary or metastatic pulmonary neoplasia. Given the patient's immunosuppression due to biologic therapy, the differential diagnosis included pulmonary tuberculosis. This diagnostic possibility was ruled out in view of the negative Mantoux and IGRA results, as well as the lower and single location of the nodule, which differed from the usual behaviour of tuberculosis.

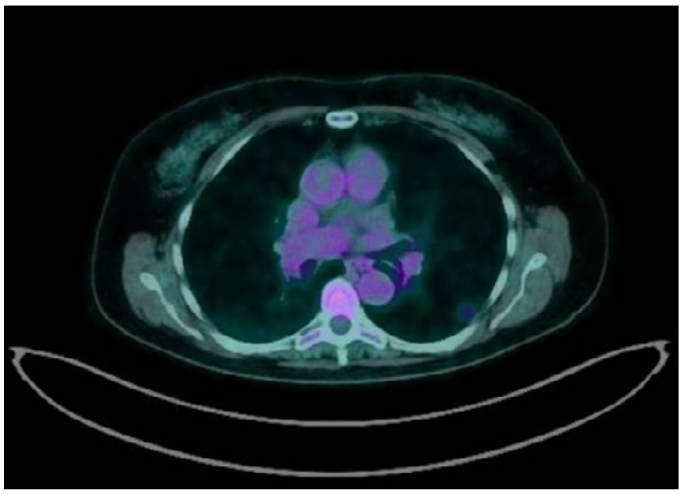

Figure 2. ***Thoracic cross-sectional PET-CT scan showing a 12mm hypermetabolic pulmonary nodule in LIL. No other findings suggestive of macroscopic neoplastic lesions or high metabolic grade were observed.***

In view of these findings, the case was presented to the multidisciplinary committee for thoracic tumours and a decision was made to perform surgery consisting of atypical resection of the LIL nodule with intraoperative analysis and, depending on the results, to decide to extend the resection. The results showed lung fragments with necrotising granulomas and surrounding hyalinising fibrosis, compatible with an uncontrolled active UC EIM, ruling out neoplastic disease.

Following the anatomopathological findings, it was decided to change the biological target to Ustekinumab due to the previous failure of Infliximab and Vedolizumab as advanced therapies, as well as other conventional treatments. In addition, given the reduced lung capacity after resection, the patient was instructed on the use of inhalers and measures to improve her lifestyle were recommended.

At the last consultation review, post-surgical changes were observed in the left lung in the control chest CT scan, together with a stable RIL nodule, as described above (Figure 3). In addition, the patient has shown some clinical bowel improvement after the last change of therapeutic target, with a reduction of the stool rhythm (4-5 bowel movements per day with minimal pathological products) and analytical improvement. From the respiratory point of view, the cough she had suffered in recent months has disappeared, so it was decided to maintain the current treatment and to carry out a close multidisciplinary follow-up in the Digestive and Pneumology departments.

Discussion

The case presents several challenging clinical and therapeutic aspects that merit discussion. The presence

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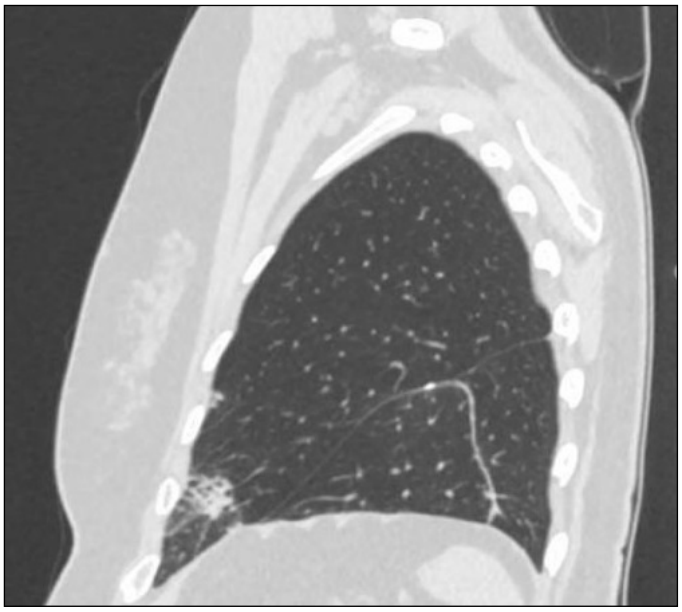

Figure 3. ***Sagittal CT scan of the chest showing post-surgical changes after atypical resection in LIL. 9 mm stable and known nodule in the right lung base.***

of long-standing UC with persistent inflammatory activity despite multiple treatments, including biologic agents such as Infliximab and Vedolizumab, underscores the complexity of managing this chronic bowel disease. The need for intravenous iron transfusions due to severe anaemia and the persistence of severe gastrointestinal symptoms, such as bloody diarrhoea and faecal urgency, significantly affect the patient's quality of life.

The incidental finding of a hypermetabolic pulmonary nodule, together with the chronic respiratory symptoms, raises concern for the possibility of primary pulmonary neoplasia, although the finding of necrotising granulomas on lung biopsy suggests possible respiratory intestinal epithelial epithelial metaplasia, compatible with pulmonary EIM, an option that should be included in the differential diagnosis in this case.

The decision to switch to Ustekinumab, due to the previous failure of the biologic agents used, highlights the importance of considering alternative therapeutic options in cases of refractory IBD. However, the persistent elevation of activity markers, such as faecal calprotectin, indicates the need for careful monitoring and possible further evaluation of treatment effectiveness.

By consulting the existing literature, this case addresses the complex and unusual extraintestinal pulmonary clinical presentation of IBD and highlights the importance of a multidisciplinary approach involving gastroenterologists, pulmonologists and thoracic surgeons, among other specialists, to address the different aspects of the disease and its potential complications.

Such multidisciplinary management is key to achieving control of the disease in the digestive and extradigestive sphere, which has a positive impact on patients' quality of life.

Bibliography

1. *Burner LP, White AM, Proksell S. Inflammatory Bowel Disease. Prim Care. 2023 Sep;50(3):411-427.*

2. *Rogler G, Singh A, Kavanaugh A, et al. Extraintestinal Manifestations of Inflammatory Bowel Disease: Current Concepts, Treatment, and Implications for Disease Management. Gastroenterology. 2021 Oct;161(4):1118-1132.*

3. *Greuter T, Vavricka SR. Extraintestinal manifestations in inflammatory bowel disease - epidemiology, genetics, and pathogenesis. Expert Rev Gastroenterol Hepatol. 2019 Apr;13(4):307-317.*

4. *Garber A, Regueiro M. Extraintestinal Manifestations of Inflammatory Bowel Disease: Epidemiology, Etiopathogenesis, and Management. Curr Gastroenterol Rep. 2019 May 16;21(7):31.*

5. *Massart A, Hunt DP. Pulmonary Manifestations of Inflammatory Bowel Disease. Am J Med. 2020 Jan;133(1):39-43.*

6. *Tejeda Taveras N, Rivera Martinez A, Kumar R, Jamil A, Kumar B. Pulmonary Manifestations of Inflammatory Bowel Disease. Cureus. 2021 Mar 31;13(3).*

7. *Barfield E, Deshmukh F, Slighton E, et al. Pulmonary Manifestations in Adolescents With Inflammatory Bowel Disease. Clin Pediatr (Phila). 2020 Jun;59(6):573-579.*

8. *Kilic Y, Kamal S, Jaffar F, et al. Prevalence of Extraintestinal Manifestations in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Inflamm Bowel Dis. 2024 Feb 1;30(2):230-239.*

9. *Gordon H, Burisch J, Ellul P, et al. ECCO Guidelines on Extraintestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2024 Jan 27;18(1):1-37.*

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