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AUTHOR QUERIES:

1. Author: Please check that the Metadata below, including Patient Details, is correct.

METADATA

Sex of patient 1:	Male
Age of patient 1:	51-70 years
Ethnicity of patient 1:	White
Region in which the patient 1 was seen/treated:	Europe (West)

TOPICS:
119 Crohn's disease
117 inflammatory bowel disease
1327 gastroenterology

Unusual association of diseases/symptoms

Chronic urticaria as a presenting symptom of Crohn's disease

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SUMMARY

Clinical presentation of Crohn's disease (CD) may be variable according to the location and the intensity of the inflammation. Some patients may have atypical symptoms which could delay the diagnosis. We report the first case of chronic urticaria related to a subclinical, complicated CD. Although the pathologic mechanism of this association was unclear in our patient, this case suggests that in patients with unexplained chronic urticaria it is opportune to investigate for a possible CD, even if there are no or few specific symptoms of intestinal inflammatory disease.

BACKGROUND

The clinical presentation of Crohn's disease (CD) can be variable according to the location and the intensity of the inflammation. Obviously, in the acute phase of CD, abdominal pain, fever and diarrhoea are the prominent manifestations which address the diagnosis. However, some patients may have mild longstanding or atypical symptoms and in these cases a delay in the diagnosis has been reported.[1] Among the atypical presentations there are those with cutaneous manifestations which are often associated with typical intestinal symptoms, but can be the sole symptom. The knowledge of these symptoms is important to avoid delay in diagnosing CD.

Here we report a case of CD diagnosed after an initial clinical presentation of chronic urticaria, a manifestation never previously described in CD patients.

CASE PRESENTATION

A 64-year-old man, affected by recurrent chronic urticaria, without angioedema, for approximately 6 months, was referred to our department of internal medicine, as an outpatient, in January 2005.

The patient also reported a weight loss of about 10 kg over the previous year, and had no gastroenterologic symptoms, fever, tiredness, fatigue and arthralgias. He had no familial history of atopia, urticaria, inflammatory bowel disease, or cancer.

The physical examination was negative, with the exception of some pruritic wheal hives on the chest and the upper limbs. Dermographism was positive.

INVESTIGATIONS

The patient did not refer physical triggers for the hives, and physical provocation tests (that is, ice cube test) were negative. A skin biopsy was performed and showed mixed cellular perivascular infiltration, composed mostly of mononuclear cells, surrounding the dermal postcapillary venules (fig 1).

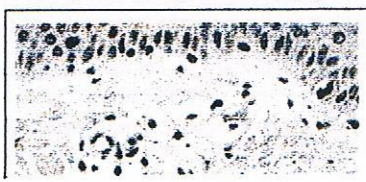

Figure 1 Histology of the skin showing interstitial oedema and inflammatory infiltration.

Table 1 shows the results of the routine blood biochemistry and immunologic assays performed 1 week after the first visit. Only erythrocyte sedimentation rate (ESR), serum C reactive protein (CRP), and absolute leucocyte count were abnormal. Furthermore, stool examinations for parasites were negative and the chest *x* ray was normal.

***Table 1** Laboratory findings at the time of the first visit*
CLICK TO VIEW

DIFFERENTIAL DIAGNOSIS

On the basis of the clinical history (severe weight loss) and laboratory abnormalities (increased ESR, CRP and absolute leucocyte count), we asked the patient to undergo further investigations. Abdominal ultrasound examination showed the presence of a suspected stricture of an intestinal loop with a thickened wall. For this reason, the patient underwent abdominal computed tomography (CT) scanning (after adequate premedication, with prednisone per os plus chlorpheniramine intramuscularly) that confirmed the presence of an important and irregular stenotic thickening of the last ileal loop and a bilateral remodelling bone lesion, predominantly sclerotic, at the sacroiliac joints due to sacroileitis. The colonoscopy showed a large polypoid lesion, with a polylobulated, irregular surface, on the ileum–caecum valve, and some aphthous erosions that totally occupied and infiltrated the upper lip of the valve, extending onto the adjacent colic and ileal wall; the polypoid lesion did not allow the exploration of the last ileal loop. Multiple biopsies were performed. Histopathology of the polypoid lesion showed severe epithelial dysplasia, whereas the surrounding colon and ileum mucosa was severely inflamed with a pronounced eosinophil infiltrate, but without granulomas or other specific hallmarks of inflammatory bowel disease.

TREATMENT

Due to the stenosing ileocaecal lesion being at risk for rapid intestinal occlusion and development of cancer, the patient was admitted to the surgery department and underwent resection of the terminal ileum plus right hemicolectomy. Macroscopic examination of the terminal ileum (22 cm) and right colic (20 cm) specimens showed, after their longitudinal section, the presence of multiple, small (1–2 mm in size) aphthoid ulcers and some longitudinal ulcers in the mucosa surface. The serosal surface revealed prominent distended blood vessels and fibrinous exudate. Histopathology showed a notable transmural flogistic infiltrate of neutrophils, along with mononuclear cells, expecially into the glandular epithelium, sometimes leading to small crypt abscesses and lymphoid aggregates, with aspects of pseudo-follicular lymphoid hyperplasia, and some epithelioid non-caseating granulomas (fig 2). In addition, there was blunting of the intestinal villi and moderate-severe dysplasia of the glandular epithelium. Isolated lymph nodes of the perivisceral fat showed normal size and only lymphoreticular activation. These findings were consistent with the diagnosis of inflammatory bowel disease with the features of CD.

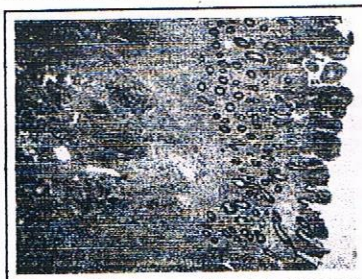

Figure 2 Histology of the intestinal mucosa of the terminal loop of the ileum showing lymphoid aggregates, pseudo-follicular lymphoid hyperplasia, and epithelioid non-caseating granulomas.

OUTCOME AND FOLLOW-UP

Five days after surgery, the patient was discharged in good clinical condition, and his chronic urticaria healed completely without any therapy. Two weeks later, he received mesalazine (2.4 g per day) for the treatment of his asymptomatic CD. To determine the extension of the CD, the patient underwent CT enteroclysis that showed normal thickness and enhancement of the small intestine wall, in the absence of imaging of intestinal stenosis or dilation, mild hyperdensitivity of perivisceral anastomotic fat, and some lymph nodes (1.5 cm size) in the context of mesenteric fat. Oesophago-gastroduodenoscopy showed normal macroscopic findings. Serum ASCA and ANCA results were negative.

The patient has been monitored during the following 30 months and has remained asymptomatic without urticaria or gastrointestinal symptoms. ERS, CRP and absolute leucocyte count were sometimes elevated and he underwent cycles of budesonide treatment (6–9 mg/day) with consequent normalisation of the above parameters.

DISCUSSION

CD is a chronic inflammatory disorder, primarily affecting the ileum, but potentially involving any part of the gastrointestinal tract, from mouth to anus. The typical clinical presentation of CD obviously simplifies the diagnosis, but some cases are difficult to diagnose, due to the presence of atypical symptoms or exclusive extraintestinal manifestations. It is estimated that one fourth of all patients with CD will have an extraintestinal manifestation, often with aspecific inflammatory histopathologic characteristics.[2–4]

These may involve mainly the skin, the musculoskeletal system, and the eyes. The skin is the most common site for extraintestinal involvement. Estimated incidence ranges from 22–44% and includes distant cutaneous (metastatic) CD, reactive skin findings (including erythema nodosum and pyoderma gangrenosum), and nutritional skin changes.[5,6] Leucocytoclastic vasculitis, with the appearance of urticarial vasculitis, neutrophilic dermatosis, cutaneous polyarteritis nodosa, and epidermolysis bullosa acquisita have also been described.[7,8]

Here we report a case of chronic urticaria, without the clinical characteristics of a physical urticaria and the histological appearance of an urticarial vasculitis, related to a subclinical, cryptic, complicated CD. We think that the concurrent presence of CD and chronic

urticaria might be causative, supported by the clinical observation of the immediate disappearance of the cutaneous manifestations following surgery and during the entire follow-up period, under specific treatment for CD, without antihistamines and/or steroids.

It is known that chronic urticaria is not linked to an IgE mediated mechanism and, in fact, our patient did not show elevated serum IgE values. Occult infections have been associated with chronic urticaria.[9] These include viral, bacterial and parasite infections (including *Helicobacter pylori*), which should be treated appropriately, but our patient did not show any infections.[10–12]

However, it is known that non-infectious chronic inflammatory processes have also been identified as causing chronic urticaria in some patients—in particular, autoimmune disorders (for example, systemic lupus erythematosus), and neoplasmas.[13,14] This seems to be the case in the patient we describe here. To our knowledge, this is the first report of an association between CD and chronic urticaria, although there are a few reports on the association between ulcerative colitis, another inflammatory bowel disease, and chronic urticaria.[15–17] Obviously, the pathogenic mechanism linking these two diseases is difficult to clarify, although it has been hypothesised, in the case of inflammatory mucocutaneous manifestations, that the pathogenesis is an influx of mononuclear cells activated in the gut, but homing aberrantly to the involved extraintestinal organs.[18]

Interestingly, the patient we describe showed another asymptomatic extraintestinal manifestation: the sacroileitis, revealed by the abdominal CT scan.[19]

It is also very interesting that our patient was never referred because of his gastrointestinal symptoms and signs, even if the lesions presented a very high risk of intestinal occlusion. Indeed, he turned to physicians only for his skin problem, and the diagnosis of CD was accidental and totally unexpected.

In addition, CD carries an increased risk of developing colorectal cancer. In our patient the presence of a polypoid lesion at the ileum–caecum valve with severe dysplasia determined a high risk of cancer, and we can affirm that the colon resection avoided the progression to cancer of the disease and improved the prognosis.[20]

In conclusion, this case suggests that, in the presence of chronic urticaria, especially if associated with certain alarm signs (such as weight loss) and laboratory findings (in our patient, elevated ESR, CRP and absolute leucocyte count), the search for possible involvement of CD is opportune, even if there are no or few specific symptoms of intestinal inflammatory disease. Gastroenterologists may be able to make an important contribution to the differential diagnosis in these patients.

LEARNING POINTS

- Clinical presentation of Crohn's disease (CD) may be variable, according to the location and intensity of the inflammation.
- Some patients affected by CD may have atypical, extraintestinal symptoms, with few or no specific gastrointestinal symptoms, which could delay the diagnosis.
- In patients with an unexplained chronic urticaria, especially if associated with some alarm signs (such as weight loss, poor response to antihistamine plus steroid therapy) and laboratory findings (elevated ESR, CRP and absolute leucocyte count), it is appropriate to investigate for possible CD, even if there are no or few specific symptoms of intestinal inflammatory disease.

Competing interests: none.

Patient consent: Patient/guardian consent was obtained for publication

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