EDITORIAL

CROHN'S DISEASE AND EXTRA INTESTINAL GRANULOMATOUS LESIONS

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Crohn's disease (CD) is an inflammatory bowel disease with a multifactorial etiology. Clinical features include mucosal erosion, diarrhea, weight loss and other complications such as formation of granuloma. In CD, granuloma is a non-neoplastic epithelioid lesion, formed by a compact aggregate of histiocytes with the absence of a central necrosis, however, the correlation among CD and the formation of granulomas is unknown. Many cases of granulomas in the extracellular site, related to CD, have been reported in the literature. These granulomas, at times, represented the only visible manifestation of the pathology. Extra intestinal granulomas have been found on ovaries, lungs, male genitalia, female genitalia, orofacial regions and skin. From the data in the literature it could be hypothesized that there is a cross-reaction of the immune system with similar antigenic epitopes belonging to different sites. This hypothesis, if checked, can place CD not only among inflammatory bowel disease but also among inflammatory diseases with systemic involvement.

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by a chronic inflammatory process. The etiology of CD is multifactorial and involves a combination of genetic and environmental factors. The set of these factors generates a condition known as dysbiosis that, by altering the eubiotic equilibrium of the intestinal flora, leads to a continuous and massive activation of the lymphoid tissue associated with the intestine (GALT) (1, 2), and the establishment of a chronic inflammatory state, characterized by the release of various chemical mediators of inflammation, such as heat shock proteins (HSP) (2, 3).

CD involves the entire gastrointestinal tract from the mouth to the anus and manifests itself with clinical features including mucosal erosion, mucus-bloody ulcers, diarrhea, weight loss, and abdominal pain (1-3). Among the complications of the disease, the most important are predisposition to dysplasia and colorectal cancer (due to the generation by TNF-alpha of a metaplasic alteration of the genetic material of the enterocyte and/or colonocyte), visceral stenosis and onset of granulomas (4).

This article focuses on the general

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characteristics of the granulomatous lesion in Crohn's disease, analyzing and discussing possible immunopathological phenomena leading to granuloma formation.

Granulomatous lesions in CD

Granuloma isanon-neoplastic lesion whose potential causes can be broadly classified as infections or non-infectious immune reactions (4-6). It is caused by a cell-mediated immune reaction to harmful substances and infectious agents that resist rapid immune destruction and are "seized" to prevent damage to the surrounding tissue. Granuloma formation is a chronic inflammatory reaction, and is triggered by a flogistic process leading to activation of T helper 1 lymphocytes and recruitment of macrophages and other inflammatory cells in the site of the lesion. Inflammation gradually destroys the harmful agents, creating debris and forming scar tissue (5). Lymphocytes are, in turn, encircled by fibroblasts that, always under the stimulus of TNF-α, produce extra-cellular matrix, surrounding and isolating the antigens (6).

After some antigen exposure and processing, the release of IFN-γ, TNF-α, and IL-2 (5, 6) allows for activation of macrophages, immune cell recruitment, epithelioid cells and giant cells as well as greater T cell proliferation (5, 6) arranged in this order from the center to the periphery (Fig. 1).

Regarding their histological features, granulomas may be of varying morphological appearance, most commonly epithelioid (4). An epithelioid granuloma is a compact aggregate of histiocytes (epithelioid cells) with or without giant cells, with no central necrosis and with the formation of histiocyte aggregates located in the most superficial part of the mucosa or associated with damaged crypts (7). Although not found in all patients with CD, granuloma, given its incidence, could be considered a pathognomonic element of the disease (6, 7).

The formation of granulomas in CD is currently a topic of discussion in the literature, as such, its symptomatology often overlaps with that of other pathologies. Generally, a CD granuloma has the following characteristics: (i) the presence of approximately 0.75 granulomas per section with a maximum width of 95 μm; (ii) microgranulomas at the inflammation sites; (iii) location of granulomas at the sigma rectum junction; and (iv) no necrosis in the center of the granuloma (7).

Extra intestinal granulomatous lesions related to CD

Although the CD-associated granuloma is found in the intestinal environment, there are numerous cases of extra intestinal granulomas associated with CD. Table I summarizes some examples of cases found in literature.

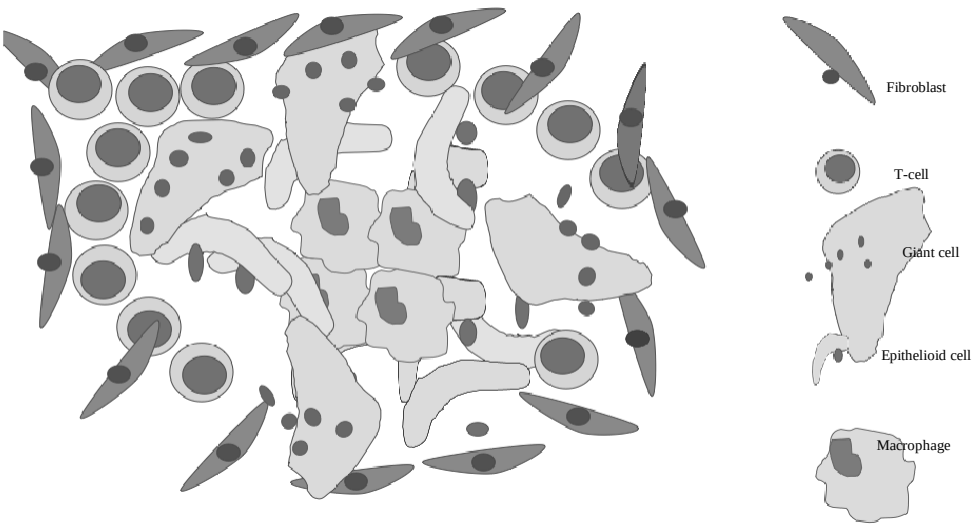

Fig. 1. *Cell infiltrates within a granuloma. From the center to the periphery, there are macrophages, epithelial cells, giant cells and T cells, surrounded by a layer of fibroblasts.*

Ovarian

The literature (among 1975 and 2015) reported 15 cases of ovarian cancer associated with CD. In most cases, an ovarian granulomatous lesion was derived from intestinal-ovarian fistulation, whereas, in one case, there was absence of fistulation and development of ovarian granuloma with an intact capsule (8).

Cutaneous

CD granulomatous lesions were found in patients with psoriasis and suppurative Hidradenitis (HS).
In relation to psoriasis, a single case was reported in which a patient with CD had skin lesions with histopathological features of psoriasis and granulomatous inflammation (9).

In relation to HS, there are three HS cases of patients who then developed CD. It is a pathology that produces perianal skin lesions clinically indistinguishable from CD. It is also important to note that, especially in a 38-year-old patient, axillary and perianal lesions were observed in areas not affected by HS-related flogos and presumably of epithelioid granulomatous attributable to CD (10).

Pulmonary

CD-related granulomatous lung involvement has been highlighted by two cases reported in the literature. The first case concerned a pediatric patient (11 years old) with a persistent symptomatology of the respiratory tract (cough and dyspnea) that did not respond to any type of drug. Pulmonary nodules were detected by CT scan and subsequently subjected to biopsy. The histopathology highlighted the granulomatous nature of these nodules, with features similar to those of a CD granuloma. The presence of CD was subsequently confirmed (11). The second case concerned a 44-year-old patient with recurrent pneumonia. Diagnostic investigations highlighted the presence of pulmonary nodules due to granulomatous lesions to be ascribed, in the first instance, to sarcoidosis. However, subsequent diagnostic investigations demonstrated a chronic inflammation of the intestine compatible with CD diagnosis (12).

Orofacial

Oral CD manifestations are well covered in the literature (1) and some studies have highlighted

Table I. *Summary of extra intestinal granulomatous lesions related to CD.*

Localization	Age	Intestinal involment (Yes/No)
Ovarian	Variable	Y
Skin	44	Y
Skin	38	Y
Pulmonary	11	Y
Pulmonary	44	Y
Lips	Variable	Only two cases (out of 3)
Penis and scrotum	18	Y
Ano – genital	21	Y
Vulvar	47	N
Vulvar	Variable	Only one case (out of 3)
Orofacial	Variable	Y
Orofacial	14	Y

the appearance of granulomatous CD lesions in the orofacial region. A first study describes three cases of patients with granulomatous cheilitis as a CD presentation. Two of the three patients also had intestinal involvement with typical CD lesions, but one patient had lips lesions as the only manifestation of the disease. Another study describes five pediatric cases (7 to 15 years of age) with non-caseous granulomatous in the oro-facial region. In two patients, the diagnosis of CD was prior to the discovery of granulomas, while in the other three the diagnosis of CD was made within 3 to 24 months after the discovery of orofacial involvement (13). A third study reports the case of a 14-year-old patient undergoing histological examination of orofacial tissues, which showed the presence of granulomas in giant cells. In the same patient, a condition of sideropenic anemia was also been reported, suggesting the endoscopic examination of the colon. Colonoscopy was positive for CD granulomatous colon lesions (13).

Male genitalia

The first case of male genitalia involvement in CD describes an African-American patient suffering from CD (diagnosed at age 8 years) with swelling of the penis. He underwent surgery for circumcision and lymphangectomy of the penis. Histological examination showed interstitial edema and granulomas, leading to a metastatic CD diagnosis. A second study describes 25 patients with history of penile and scrotum swelling caused by ano-genital granulomatosis (AGG). The presence of abdominal pain in the same patients led to a diagnosis of CD, thus correlating AGG to CD (14).

Female genitalia

Report studies show a case of a 47-year-old patient with vulvo-perineal granulomas being the only manifestation of the CD (15), and three cases of vulvar giant cell epithelial granulomas. In two of the three cases, there was no intestinal involvement and vulvar granulomas were the only manifestation of the CD (16).

In conclusion, based on the reported studies in the literature, one could say that patients who develop granulomas are those with a more severe form of the disease which is confirmed by the fact that one patient may be negative at the time of diagnosis and positive at a later stage. Such a fact suggests that the presence of granuloma is related to a greater severity of the pathophysiological course of the CD. The presence of inflammatory-granulomatous lesions could represent the first signs of the disease. In fact, in many of the cases described, the extra-intestinal manifestations of CD appeared before those of the intestines. On this basis, one could also formulate a hypothesis regarding the pathogenesis of extraintestinal CD manifestations. In particular, one could hypothesize that there are cross-reactions of the immune system with similar antigenic epitopes belonging to different sites. This hypothesis, if checked, can place the CD not only among IBD's but also among inflammatory diseases with systemic involvement, however, further studies are needed in this regard.

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