Bizarre stromal cells in Crohn's disease

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Abstract

Lesions with bizarre stromal cells (BSC) have been described in many organs and, although benign, they are frequently misdiagnosed as malignancy. We present the first case of BSC in Crohn's disease with a rare submucosal topography and we review the related literature. We hypothesize that, in Crohn's disease, BSC of myofibroblastic origin may be related to the development of submucosal fibrosis.

Keywords Bizarre stromal cells, gastrointestinal tract, colon, gut, Crohn's disease

Ann Gastroenterol 2019; 32 (2): 1-4

Introduction

Bizarre stromal cells (BSC) have been reported in many different organs in association with granulation tissue, usually in benign inflammatory polyps or in ulcerated mucosa. BSC have atypical cytological characteristics with diverse shape, vesicular large nuclei with prominent nucleoli and a variable amount of cytoplasm. The differential diagnosis when they are detected in groups includes high-grade carcinoma, sarcoma or melanoma and they also have to be distinguished from cytomegalovirus (CMV)-infected cells or ganglion cells [1].

In the gastrointestinal (GI) tract, BSC have been reported in gastric ulcers, esophageal polyps in patients with reflux esophagitis, granulation tissue near surgical anastomoses, ischemic colitis, pseudopolyps in ulcerative colitis, and anal fibro-epithelial polyps [2,3]. In this case report we present an adult man with mildly active Crohn's disease of the colon, modified by treatment, and a focal collection of submucosal

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Conflict of Interest: None

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BSC. This is the first reported case of BSC in Crohn's disease and BSC with submucosal topography in the GI tract.

Case report

A 42-year-old male patient with known treated colonic Crohn's disease presented with terminal ileal stenosis with edema and inflammation of the ileocecal valve. An extensive right colectomy followed by ileostomy was performed. Histological examination showed mild distortion of colonic mucosal architecture with focal erosions and a mixed inflammatory infiltrate with an increased number of eosinophil polymorphonuclear leukocytes, and focal fibrosis and edema of the submucosa, more pronounced in the ileocecal valve. At the upper submucosal layers of the cecum, underneath eroded mucosa, a group of atypical epithelioid, spindle or stellate cells with large, hyperchromatic, polymorphic nuclei and abundant eosinophilic cytoplasm were detected. Some of the cells were multinucleated (Fig. 1). The atypical cells, in the limited number of serial sections where they were still present, were positive by immunohistochemistry for the mesenchymal marker vimentin, the majority were positive for the macrophage marker CD68, while some were positive for α-smooth muscle actin (αSMA). They were negative for endothelial markers (CD31, CD34), epithelial markers (pankeratin) (Fig. 2) and CMV. Their immunophenotype was considered indicative of macrophage, fibroblastic or myofibroblastic origin.

Discussion

In 1982, Isaacson [4] first reported BSC in inflammatory lesions of the esophagus, stomach and rectum. Since then, in addition to the GI tract, BSC have been detected in benign lesions
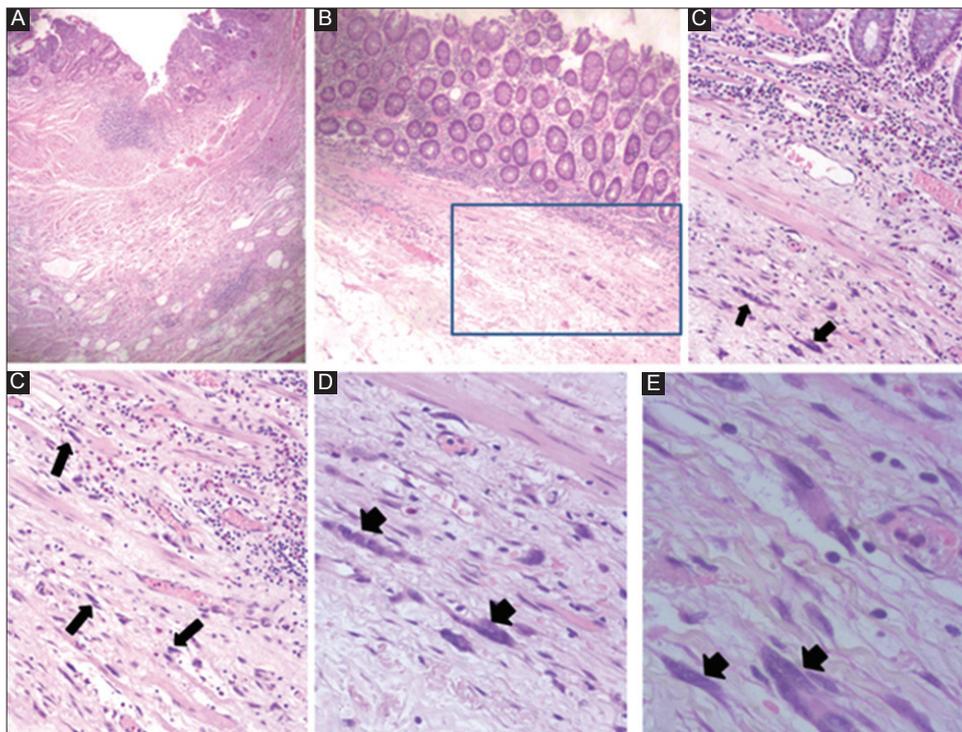
Figure 1 (A) Inflamed mucosa and fibrosed inflamed submucosa in treated Crohn's disease, hematoxylin and eosin (H&E) ×20. (B) Bizarre cells (rectangle) in the upper submucosa, H&E ×100. (C, D) Arrows show the submucosal large spindle-shaped cells in higher magnification in association with a mixed inflammatory infiltrate rich in eosinophils, H&E ×200. (E, F) Some bizarre cells are multinucleated (arrows in E), while others have large hyperchromatic polymorphic nuclei and abundant eosinophilic cytoplasm (arrows in F), H&E ×400

of the breast, female reproductive system, prostate, urinary tract, spleen, and paranasal tracts [2]. In the GI tract, BSCs have been encountered in lesions of the gastroesophageal junction, esophagus [5], in relation to gastric ulcers [2,4,6,7], in ischemic colitis [8], and in ulcerative colitis [9,10]. Inflammation appears to be the common underlying condition, regardless of lesion topography [11]. Ours is the first report of BSC in Crohn's disease and we highlight their rare submucosal topography (Table 1).

The first symptoms may include GI bleeding, epigastric pain, abdominal distension, sour regurgitation, belching, heartburn and anemia. A medical history of inflammatory bowel disease (IBD) is not uncommon [5,9]. As mentioned above, lesions containing BSC may occur throughout the GI tract, but the distal part of the esophagus, particularly the region next to the gastroesophageal junction, and the large intestine are most commonly affected [2]. BSC may present within intramural masses or large polyps, rather than within a small polyp or ulcer, which is the typical presentation of pseudomalignant lesions. BSCs have also been identified within ischemic mucosa since the widespread use of endoscopy of GI disorders has increased the frequency with which these lesions are encountered [4,12,13].

On histology, BSC appear as atypical, spindled, stellate, epithelioid or large round cells within inflamed *lamina propria* or granulation tissue. They have abundant amphophilic or eosinophilic cytoplasm, vesicular nuclei and large eosinophilic nucleoli, which sometimes may be difficult to differentiate from CMV inclusions. Immunohistochemical stains for CMV, however, are always negative [8], as in our case.

BSCs are usually dispersed in a zone under ulcerated or regenerating mucosa but have not been reported in the submucosa to date. BSC most likely represent reactive fibroblasts or myofibroblasts [7,14], an observation strengthened by the fact that they stain strongly for vimentin and sometimes for αSMA. Shekitka *et al* showed that BSC were positive for vimentin in 20 and αSMA in 7 of 23 cases [2]. In the majority of the studies, Ki-67 immunostaining highlighted their low proliferative rate (labeling index <1%). Mitotic figures are very uncommon and atypical mitoses are absent, while no cytoplasmic mucin or glycogen is detected with special histochemical stains. BSC sometimes lie within inflammatory exudate with associated epithelial elements and may disappear on follow up. Immunostaining for pankeratin is essential to rule out carcinoma.

If the histologic changes are not absolutely convincing, or if the surgical pathologist does not feel confident about establishing a definite benign diagnosis, it is advisable to repeat the biopsy, since it has been reported that atypical regenerative changes can decrease notably or even disappear within 3-5 weeks. A repeat biopsy, clinical follow up and subsequent endoscopic studies are best recommended. Isaacson presented a series of 10 cases in which major resections were performed unnecessarily in three patients following erroneous diagnoses of carcinoma. This is quite worrying, given the fact that a second opinion from a consultant GI pathologist was obtained for the final diagnosis. In the series of Shekitka and Helwig, epithelial or mesenchymal malignancy was incorrectly diagnosed in 6

Table 1 Case reports of bizarre stromal cells in the gastrointestinal tract

| Author	Year	Ref.	n	Organ involved/disease
Iliakopoulos *et al*	2019		1	Colon
Xinqing *et al*	2017	[5]	9	Esophagus
Piana *et al*	2014	[14]	1	Esophagus
Al-Oqaily *et al*	2013	[20]	1	Esophagus
Dhungel & De Petris	2013	[11]	2	Esophagus
Wolf *et al*	2013	[16]	1	Esophagus
Kamat *et al*	2006	[10]	1	Colon/ulcerative colitis
Serra & Chetty	2005	[8]	3	Colon/Ischemic bowel disease
Gill *et al*	2003	[7]	2	Esophagus
Shekitka & Helwig	1991	[2]	33	Esophagus (n=2), gastroesophageal junction (n=4), stomach (n=5), large intestine (n=21), anal canal (n=1)
Isaacson *et al*	1982	[4]	7	Esophagus (n=2), stomach (n=4), rectum (n=1)
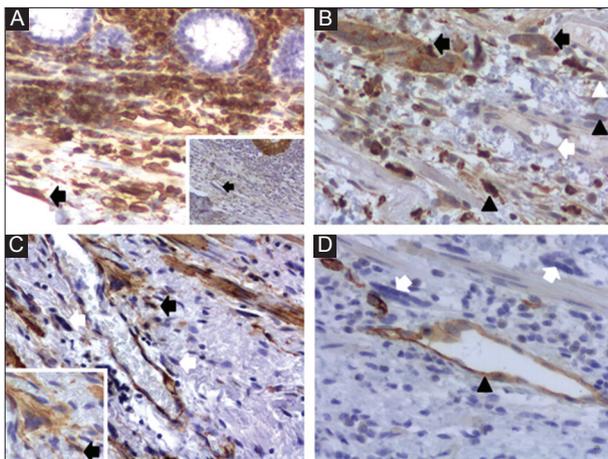
Figure 2 Immunohistochemical characteristics of bizarre submucosal cells (3,3'-diaminobenzidine chromogen): (A) Positivity for vimentin (arrow, ×400) and absence of immunoreactivity for pankeratin (inset, arrow, ×200) highlights their mesenchymal nature. Lymphocytes and epithelial crypt cells (inset, upper right) act as internal positive control for vimentin and pankeratin, respectively. (B) Multinucleated bizarre cells (black arrows) and some of the mononuclear bizarre cells (black arrowheads) are positive for the macrophage marker CD68, while occasional bizarre cells (white arrowhead) and endothelial cells (white arrow), as expected, are negative (×400). (C) Occasional immunopositivity for α-smooth muscle actin (αSMA) (black arrow), while most bizarre cells are αSMA-negative (white arrows), ×400. Inset shows an αSMA-positive mononuclear bizarre cell (black arrow) in higher magnification. The adjacent multinucleated cell is negative for αSMA (×600). Smooth muscle cells from the *muscularis mucosae* (upper right) serve as internal positive control. (D) Submucosal bizarre cells (white arrows) are negative for the endothelial marker CD34, while the endothelial lining of a capillary (black arrowhead) and smooth muscle fibers (upper right) and inflammatory cells serve as internal positive and negative controls, respectively. Immunostaining for cytomegalovirus was negative (not shown)

of 33 (18%) cases with BSC. When 24 of these patients were followed up for an average of 13 months, none of the lesions with BSC progressed to malignancy [2].

In our case of Crohn's colitis, some of the submucosal BSC expressed αSMA in association with vimentin, indicating a possible myofibroblastic origin. Myofibroblasts are found in sites of inflammation in response to chemotactic gradients and are involved in tissue growth and repair, peripheral immune tolerance, inflammation and fibrosis. They produce extracellular matrix (ECM) molecules, resulting in tissue fibrosis as a consequence of chronic inflammation and injury associated with IBD, mainly Crohn's disease [17]. It is possible that, in our case, BSC of myofibroblastic origin along with classical myofibroblasts were responsible for the submucosal fibrosis observed histologically. Newly proposed therapy for Crohn's disease-related fibrosis is now directed toward the immune aspect of this complex chronic inflammatory disorder. New treatments involve disruption of inflammatory signaling pathways that lead to fibrocyte/activated myofibroblast migration, and stem cell therapy to replace these ECM-producing cells and/or enrich the inflammatory microenvironment with less profibrogenic mesenchymal cells [17-19].

In conclusion, BSC in GI lesions may lead to a major diagnostic pitfall. Endoscopic, histological and immunohistochemical characteristics are helpful for an accurate diagnosis. Awareness of the presence of these atypical cells can prevent unnecessary operations, thus having a significant impact on patients' quality of life.

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