Eosinophilic Venulitis of Colon Presenting as Ileocecal Mass

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Abstract. Reports of eosinophilic infiltration of the colon causing obstruction are few. It is even less common to find associated extensive intestinal venulitis, which is similar to and lumped together with so called Mesenteric Inflammatory Veno-Occlusive Disease (MIVOD) or Self-Limited Intestinal Venulitis. Eosinophilic necrotizing lymphadenitis, such as what we report here, has never been reported in association with this disease.

A 41-year-old female presented with cramping lower abdominal pain, hematochezia, nausea, and vomiting. Computed tomography revealed the presence of the mass and thickening of the illeocecal wall. Endoscopy confirmed a cecal mass with surface ulceration suggestive of cecal adenocarcinoma. Patient underwent right hemicolecctiony with the clinical and radiologic diagnosis of adenocarcinoma. Microscopic examination of the resected bowel showed an ulcerated mass in the cecum composed of markedly edematous tissue showing transmural eosinophilic infiltration and extensive eosinophilic and lymphocytic venulitis with and without thrombosis. This was associated with a necrotizing lymphadenitis.

Key words: eosinophilic colitis, cecal mass, venulitis, necrotizing lymphadenitis, mesenteric inflammatory veno-occlusive disease

Introduction

A moderate increase in the number of eosinophils in colonic biopsies is common and nonspecific. Normal tissue eosinophils vary widely in individuals, typically comprising approximately 3% of the cells in the lamina propria [1]. The number of eosinophils also varies between different segments of the colon, ranging from <10 eosinophils per high-power field in the rectum to >30 in the cecum. Thus, the location of the biopsy is crucial for interpretation of the findings [1, 2]. Pathologically excessive infiltration of the colonic wall by eosinophils indicates the possibility of eosinophilic colitis. However, a definitive diagnosis requires the presence of eosinophilic cryptitis or crypt abscesses and infiltration beyond the mucosa.

The presentation of eosinophilic colitis as a tumor is unusual [3-6]. Association with venulitis [6-8] and thrombosis causing ischemic [8-10] mucosal changes is rare. The presence of necrotizing lymphadenopathy has never been reported.

Case Presentation

A 41-year-old female presented with acute onset of cramping right lower abdominal pain associated with bloody bowel movements, nausea, and vomiting. She denied fever, diarrhea, weight loss, joint pain, or any similar episode in the past. Her past medical history was significant for allergies to dust and mites, and a recurrent genital herpes infection for which she had received acyclovir three times. Her family history was unrevealing for any colorectal illness.

Upon physical examination, she was afebrile with normal vital signs. She had no mucocutaneous lesions. Her abdomen was soft and non-distended, with moderate right lower quadrant tenderness but no rebound tenderness, guarding, or rigidity. There was no hepatosplenomegaly, and bowel sounds were normal. There was no lymphadenopathy, rash, or external fistula.

Her stool was positive for occult blood and negative for fecal leukocytes, bacteria, ova, and parasites. Stool culture grew normal fecal flora. Laboratory investigations included hemoglobin of 11.0 g/100ml with normal red blood cell indices and a leucocyte count of 6900/mm3 with 2% eosinophils. A computed tomography (CT)-scan of the abdomen showed a large segment of markedly thickened bowel extending from the right lower quadrant and involving the entire ascending colon. The thickened piece of bowel in the right lower quadrant measured approximately 11 x 4 cm. Mucosal hyperemia
and a 13 x 11 mm para-aortic lymph node was noted. Subsequently, the patient had a colonoscopy that revealed a large (10 cm), polypoid mass with friable appearance in the ascending colon, nearly occluding the lumen. The scope could not be advanced further, and the cecum could not be visualized. Biopsies from this mass showed friable necrotic tissue and were non-diagnostic. An upper GI endoscopy was done with multiple random gastric and duodenal biopsies, all of which were normal.

She underwent exploratory lapatomy with a preoperative diagnosis of a right colon mass. A mass was noted in the submucosa of the cecum, separate from the ileocecal valve and the appendix. No ulceration was seen. Few reactive lymph nodes were seen, but there was no evidence of malignant ascites, peritoneal carcinomatosis, omental implants, or involvement of the liver or other intra-abdominal viscera. A right hemicolectomy with complete resection of the mass was performed, and the resected bowel was sent for pathologic examination.

Post-operative course was unremarkable, but the patient continued to have intermittent abdominal pain for which a steroid trial (Prednisone, tapered over 2 weeks) was given without much symptomatic relief. She continued to take pain medications for abdominal pain. She did not have any diarrhea or weight loss. After being followed for about a year after surgery, she was lost to follow-up.

**Pathological Findings**

The specimen was a segment of terminal ileum, cecum and ascending colon. Gross examination showed an exophytic superficially ulcerated mass 2.5 cm from the ileocecal valve, measuring 6.5 cm at its largest diameter. It had a rubbery consistency and was 1.5 cm thick within the mucosa. The rest of the colonic mucosa was edematous. The serosa was umbilicated under the tumor and was extensively covered by fibrinous exudates and adhesions.

Microscopically, the tumor was an inflammatory mass composed of markedly edematous fibroconnective tissue infiltrated by eosinophils and lymphocytes. The tumor had an appearance not unlike that of an allergic nasal polyp. Most of the eosinophilic infiltration was in the various layers of the colonic wall. Mucosa showed patchy eosinophilic infiltration without thrombosis. Elastic Van Gieson and actin immunoperoxidase stains confirmed the venous nature of the involved vessels. Arteries were spared. These lesions were characterized by mild to moderate eosinophilic and lymphocytic infiltration of the wall of veins (Figures 1 C and D) with the occasional focus of fibrinoid necrosis. The thrombotic process lead to ischemic injury noted in the mucosa (Figure 1B). Perivascular...
connective tissue was usually involved, showing a cuff of lymphocyte and eosinophil condensation around the venules. The lumen of the involved vessels showed fibrin thrombi in various stages of organization, from months to days in duration (Figures 1 C, E, and F). Focally, endothelial hyperplasia was prominent (Figures 1 E and F, and 2 A and B). In some of these veins, no fibrin was present and partial endothelia hyperplasia forming a somewhat polypoid, nodular mass with partial obstruction of the lumen was noted (Figures 2 A and B). These veins often showed infiltration of the wall by eosinophils and lymphocytes. The lesion was widespread and was noted throughout the entire colectomy specimen but was most severe in the area of tumor where the largest veins were involved. Serosal involvement was severe and was associated with extensive serositis. The adipose tissue adjacent to areas of venulitis showed panniculitis and extensive fibroblastic proliferation, eosinophilic infiltration, and lymphocytic infiltration. However, plasma cells, neutrophils, and immunoblasts were strikingly absent.

Several enlarged mesenteric lymph nodes were present. One showed an area of necrosis associated with much fibrin deposition and eosinophilic infiltration typical of necrotizing lymphadenitis (Figures 2 D and E). No obvious associated vasculitis was noted in the node.

Discussion

Eosinophils are the key effector cells of the innate immune system within the GI tract. These cells are customary inhabitants of the gastrointestinal tract, except for the esophagus [11]. Eosinophilic colitis (EC), first described by Kaijser in 1937 [12], is a rare manifestation of eosinophilic gastroenteritis, which does not appear to be increasing in prevalence, in contrast to recent trends seen in esophageal disease. EC seems to be a heterogeneous entity [2]. Since secondary eosinophilic inflammation may occur in numerous gastrointestinal disorders, the true incidence and prevalence of primary EGID - including eosinophilic colitis - remains largely unknown [1, 2]. In the colon, eosinophilic infiltration may be seen in allergic proctocolitis of infants. In adults, eosinophilic infiltration is less defined and may be found in different conditions including drug-induced colitis, even though the pathological findings are often inconsistent. These disorders are classified into the primary subtype, which includes the atopic and nonatopic variants, and the secondary subtype, which is divided into systemic eosinophilic disorders and non-eosinophilic disorders.
In 1970, Klein et al subdivided the disease based on the layer of intestinal wall most extensively infiltrated by eosinophils; classifications included the mucosa-predominant form involving mucosal dysfunction, the muscularis-propria-predominant form manifesting symptoms of obstruction and showing bowel wall thickness upon imaging, and the serosal-predominant form, distinguished by the presence of eosinophilic ascitis [14,15]. Obstructive presentations (like cecal volvulus and intussusception) seem to be more common in adults than in children [11,16]. EC can also masquerade as a tumor [3-5].

Diagnosis of eosinophilic colitis usually occurs after colonic biopsy. The endoscopic gross appearance of eosinophilic colitis is nonspecific and includes patchy, erythematous, friable, nodular hyperplasia and occasionally ulcerated mucosa, and is thus too nonspecific for diagnosis [13]. Histologic examination often reveals that the architecture of the mucosa is generally preserved, helping to distinguish EC from other colitides [11], since there are focal aggregates of eosinophils in the lamina propria. In addition, definitive histologic diagnosis requires invasion of the crypt epithelium or lumen (eosinophilic cryptitis and crypt abscesses), involvement of muscularis mucosa, or subserosa [1]. The distinctive features of this case are the eosinophilic infiltration of the wall of medium- to small-size veins in association with thrombosis in different stages of organization, and the presence of necrotizing lymphadenitis. It is noteworthy that without the venulitis and necrotizing lymphadenitis, the present case would be a classic case of pure eosinophilic colitis.

Ultimately, the diagnosis of eosinophilic colitis might become a diagnosis of exclusion. Thus, careful clinical and diagnostic review should exclude chronic inflammatory bowel disease, hypereosinophilic syndrome, and vasculitides. Serological and stool studies may help eliminate infectious causes of eosinophilic infiltration. Evaluation of IgE levels may help in assessing allergen involvement. Careful dietary review and observation should be undertaken [11].

EC may masquerade as a tumor [3-7], as was evident in our case. Mesenteric inflammatory veno-occlusive disease (MIVOD), first described in 1994, is a vasculitis of unknown etiology limited to the mesenteric area, affecting veins and venules exclusively and sparing arteries. Histologically, the lesions show lymphocytic and/or necrotizing, sometimes granulomatous phlebitis, and chronic lesions of myointimal hyperplasia reducing the lumen of the veins [8]. In a review of 6 cases by Saraga et al, phlebitis was found predominantly in subucosa, as well as in the tumoral mass [10]. In 1999, Stage et al described a case of mesenteric phlebitis with marked eosinophilic infiltration [8].

Patients with MIVOD are usually under 50 years old and healthy prior to presentation. They typically present with abdominal pain, mucus per rectum, or bloody diarrhea, of variable duration [17]. The etiology of MIVOD is incompletely understood. Cytomegalovirus infection [18] and certain drugs have been implicated as etiologic agents in case reports [19,20].

Histologic examination of our case revealed necrotizing lymphadenitis (Figures 2 D and E) in addition to eosinophilic venulitis. Cases of mesenteric necrotizing lymphadenitis have been reported as a primary condition presenting as appendicitis [21-23] or as associated with systemic lupus [24,25], and in other locations in association with the infections CMV [18], EBV [26], human herpes-6 [27,28], and in phenytoin–induced hypersensitivity syndrome [29]. However, to our knowledge, there has not been any report of this finding associated with intestinal venulitis, MIVOD or eosinophilic enterocolitis. Most EC cases of this type, including ours, have been diagnosed on surgical full-thickness biopsy or resection performed for obstruction or suspicion of malignancy [11].

There seems to be a connection between eosinophilic infiltration in tissue and the presence of edema, fibrosis, and endothelial cell changes characterized by plump endothelial cells, hyperplasia in the form of cushions within the lumen of veins, granulation-like capillary formation, and fibrosis of surrounding connective tissue.

One notes this connection in other disorders; several seemingly unrelated and unusual diseases share most of these features, for example: Epithelioid Hemangioma/Histiocytoid Hemangioma, Angiolymphoid Hyperplasia with Eosinophilia, Kimura’s Disease, Angiosarcoma, Mesenteric Inflammatory Veno-Occlusive Disease and Intestinal Venulitits. These disorders have other
features in common: regional lymphadenopathy containing eosinophils was reported in Epithelioid Hemangiomia, Kimura’s Disease, Angiolymphoid Hyperplasia with Eosinophilia, and eosinophilic gastroenteritis and necrotizing adenopathy, which is reported for the first time in the present case [28,30-32]. These disorders also have similar, perhaps etiologic, associations with immunologic abnormalities such as SLE, scleroderma, and viral infections including CMV, EBV, Herpes, and HIV.

The present case shows many morphologic similarities with Angiolymphoid Hyperplasia with eosinophilia and Kimura’s Disease, in which the endothelial lesion and lympho-eosinophilic infiltration are similar. However the adenopathy in Kimura’s and angiolymphoid hyperplasia with eosinophilia are typically characterized by prominent germinal centers, vascular proliferation, and eosinophilic infiltration without necrosis. Kikuchi-Fujimoto Disease is also characterized by necrotizing lymphadenitis [28,31,32]. The lesions characteristically lack plasma cells and neutrophils, as in the present case. The presence of eosinophilic necrotizing lymphadenitis in our case may indicate similarity in pathogenesis with Kikuchi-Fujimoto Disease. Kimura’s, angiolymphoid hyperplasia with eosinophilia, and Kikuchi may be associated with skin lesions as well as with herpes simplex and EBV infections. Our patient had a history of herpes simplex.

Pathologically, in our opinion, there are three related but seemingly separate processes involving the vessels. The obvious one is eosinophilic and lymphocytic vasculitis (Figures 1 C and D), the second is myointimal hyperplasia (Figures 2 A, B, and C), and the third is thrombotic complication of one and two with fibrin deposition and various degrees of organization (Figures 1 C, E, and F). Organization of thrombus is typically characterized by fibroblastic and intimal cell hyperplasia within the vessel – but not by smooth muscle hyperplasia. There is often perivascular fibroblastic proliferation in the surrounding connective tissue of afflicted vessels (Figure 2 F), and it is often mixed with eosinophilic infiltration. The proliferating cells show endothelial marker CD34 positivity, but none or weak smooth muscle actin marker reactivity. These cells appear to be fibroblasts and not muscular. Their association with eosinophils suggests a fibrotic reaction to eosinophilic activation and degranulation.

In most vessels, the three aforementioned processes are not fully distinct; however, in vessels in which they are, the conclusion that they may be separate but overlapping processes may be drawn. In the literature, one occasionally finds entities that show these in isolation; some are characterized by lymphocytic infiltration only, not including eosinophils. There are rare cases of non-inflammatory myointimal hyperplasia. The association of venulitis with eosinophilic infiltration and the relative sparsity of lymphocytic infiltration distinguishes our case to a certain extent.

In general, intestinal vasculitis may occur as part of a systemic vasculitides. However, in these cases the inflammation involves the arteries. Venulitis alone may be found in cases with systemic lupus erythematosus [24,25], Churg-Strauss syndrome [33], or in Behcet’s disease [34,35].

Flaherty et al. [9] and Saraga et al. [10] described the ischemic lesions associated with vasculitis and thrombosis of veins and venules with the sparing of arterial tributaries involving the large bowel and small bowel. The vascular inflammatory infiltrate varied in composition from predominantly lymphocytic to neutrophilic with fibrin deposition (necrotizing venulitis). Granulomatous vasculitis has also been reported in some cases. Myointimal hyperplasia with reduction of vascular lumina was frequently present in these cases [36]. It has been suggested that thrombosis is more likely a consequence of the phlebitic and venulitic lesions and the cause of the ischemic intestinal injury (similar to Figure 1 B) rather than secondary to it. Secondary myointimal hyperplasia (similar to Figures 2 A and B) eventually further reduces mesenteric vascular flow and consequently contributes to increased ischemic intestinal damage [9,10]. Fibrin thrombi are found in inflamed veins and venules at different stages, from recent to organized, indicating a chronic pathway. The etiology of this clinicopathological entity remains to be elucidated, and no association with a definite predisposing cause was identified. Treatment of older patients may require medication, because IgE-associated triggers are rarely identified even in the atopic
variant. Although well-designed clinical trials are lacking, short courses of topical or systemic corticosteroids for 1-2 weeks or a 5-aminosalicylic acid appear to be efficient. In refractory cases, immunomodulator therapy with azathioprine may be required [11].

The etiology of the eosinophilic venulitis with such a dramatic presentation as in this case of an otherwise healthy middle-aged woman remains unclear. In retrospect, her history of recurrent herpes and treatment could raise the question of an association between herpes/drugs and eosinophilic venulitis. A post-infection theory could be hypothesized for future research in this area.

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