Small Bowel Pyogenic Granuloma With Cytomegalovirus Infection in a Patient With Crohn's Disease (Report of a Case and Review of the Literature)

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Abstract. *Pyogenic granuloma (PG) represents a lobular capillary proliferation commonly seen in the skin or oral mucosa. They are rarely reported in the gastrointestinal tract. The mechanism underlying PG pathogenesis is not well understood. Only one case of cutaneous PG associated with cytomegalovirus (CMV) infection has been reported in the English literature. Here, we report such a unique case of PG arising from the small bowel. A 67-year-old male, status post ileocolic resection, presented for follow-up colonoscopy because of Crohn's disease of the terminal ileum and the colon. Colonoscopy revealed inflammation at the ileocolic anastomosis as well as an 8-mm pedunculated lesion with an irregular surface in the neo-terminal ileum. Histological studies of the small bowel mucosa revealed chronic active ileitis with pyloric gland metaplasia, consistent with his clinical history of Crohn's disease. The lesion demonstrated a lobular architecture consisting of clusters of small capillaries of various sizes lined by a single layer of cytologically bland endothelial cells, and accompanied by acute and chronic inflammatory infiltrates and surface erosion/ulceration. The histological features supported the diagnosis of PG. Scattered*

viral inclusions with positive CMV immunoreactivity were present in the endothelial cells and glandular cells of pyloric gland metaplasia within the PG. To the best of our knowledge, this is the first documented case of PG with local CMV infection in patients with inflammatory bowel disease.

Pyogenic granuloma (PG), also called granuloma pyogenicum, lobular capillary hemangioma, is a benign lesion that usually occurs in children and young adults. The vast majority of PGs occur in the skin or the mucosal surface of the oral cavity (1-3). In the skin, PGs are usually rapidly growing polypoid or pedunculated reddish-brown nodules surrounded by thickened epidermis. Often, the surface of the lesions is ulcerated and the lesion bleeds easily. Histologically, PG demonstrates a lobular pattern of vascular proliferation with inflammation and edema resembling granulation tissue (4).

Compared to oral or cutaneous PGs, PGs in gastrointestinal (GI) tract are very rare and often occur in older patients (5-8). The mechanism underlying PG pathogenesis is not well understood. We herein report the first documented case of CMV infection associated PG arising from small bowel in a patient with Crohn's disease. The pathogenesis, endoscopic and pathologic diagnosis and treatment of PG are discussed.

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Key Words: Pyogenic granuloma/lobular capillary hemangioma, small bowel, Crohn's disease, cytomegalovirus (CMV).

Case Presentation

A 67-year-old male who had past medical history of hypertension, hyperlipidemia, gastroesophageal reflux disease and vitamin B12 deficiency presented for follow-up colonoscopy of Crohn's disease. His Crohn's disease involved the terminal ileum and the colon and was diagnosed following an ileocolic surgical resection for bowel obstruction in 2012.

Figure 1. Endoscopic and histological findings of PG. A: Endoscopic appearance of an 8 mm pedunculated polyp in the terminal ileum (arrow). B: Two erosive lesions representing polypectomy wound after resection. C-D: Histologically, the polypoid lesion showing pyloric gland metaplasia (C, arrows), surface ulceration, lobular capillary proliferation with intracytoplasmic and intranuclear inclusions (D, arrow) (H&E stain, C, 100 $\times$; D, 400 $\times$).

The patient has been treated with budesonide mongersen (clinical trial) for his Crohn's disease in the past. His previous follow-up colonoscopy four months ago showed a benign-appearing intrinsic moderate stenosis and moderately active disease without any lesions. The patient was currently having 3-4 bowel movements per day with fecal urgency and failed evacuation. He denied nausea, vomiting, fevers, chills, or night sweats, but reported some heartburn, mild right lower quadrant abdominal pain and 3-kg weight loss. He was currently involved in a Phase III clinical trial. The patient's lab tests were unremarkable except for mildly decreased red blood cell count $4.4 \times 10^6/\mu\text{l}$ and slightly low hemoglobin level 12.9 g/dl.

During colonoscopy, the rectum, sigmoid colon, descending colon, transverse colon and ascending colon appeared normal. Abnormalities were detected at the neo-terminal ileum and the ileocolic anastomosis. One 8 mm pedunculated polyp was

identified at the neo-terminal ileum and removed by polypectomy (Figure 1). Side to side ileocolic anastomosis was slightly narrowed but patent with inflammation. Microscopically, multiple fragments showed chronic active ileitis with ulceration. There was an inflammatory polyp with features of PG with surface erosion and ulceration. Focal epithelial healing was present. Pyloric gland metaplasia was present. No granulomas were identified. There were a few viral inclusions present in the endothelial cells in the polypoid lesion that were confirmed to be cytomegalovirus (CMV)-infected cells by immunohistochemistry. CMV positive cells were also present in the glandular cells of pyloric gland metaplasia. CD31 and ERG highlighted the cytologically bland capillary proliferation (Figure 2). Although other fragments also showed ulceration, no CMV-positive cells were seen. No dysplasia or carcinoma was identified. His blood CMV DNA quantitative

Figure 2. Immunohistochemistry. A-B: CMV immunoreactivity presents in a metaplastic pyloric glandular cell and an endothelial cell (arrows). C-D: Immunohistochemical stains for CD31 (C) and ERG (D) highlight the capillary proliferation (A, 100 $\times$; B, 400 $\times$; C-D, 200 $\times$).

polymerase chain reaction (qPCR) test was performed and reported as negative with <2.6 log copies/ml.

In a two-month follow-up, the patient was on steroids and currently having 4 bowel movements per day. He reported mild abdominal pain, but denied any fevers, chills, night sweats, nausea, vomiting, or weight loss. CMV DNA quantitation by PCR was negative.

Discussion

The mechanism underlying PG pathogenesis is not well understood. PG is an inflammatory hyperplasia related to various stimuli such as chronic local irritation, trauma, burn, hormonal imbalances, underlying arteriovenous malformation, and bone marrow transplant (9). In general, PGs could be due to infection, but no bacterial, fungal, or viral origin has well been proven. It is reported that PG patients have a higher

prevalence of *Bartonella* seropositivity (10), however, *Bartonella* spp were not detected by immunohistochemistry and PCR for *Bartonella* DNA were negative in 45 PG specimens, suggesting that PG is not associated with *Bartonella* spp infection (11). However, a case reported by Abrams showed CMV and organisms consistent with *Bartonella* were present in a cutaneous PG of a patient with acquired immunodeficiency syndrome (AIDS) (12). In our case, CMV was detected locally in the endothelial cells and metaplastic pyloric glandular cells within PG. CMV DNA qPCR in peripheral blood was subsequently performed and the result was negative. The patient's localized CMV infection is most likely due to his immunosuppression and CMV may have contributed to the formation of PG in this patient.

There are approximately 50 cases of GI PG in the English literature (13). The endoscopic appearance of PG lesions is usually a smooth and ulcerated surface that appears friable.

The color ranges from bluish-red to sanguine with a superficial white or opaque film covering. PGs can grow quickly and then stabilize in size (14). PG size was reported for 37 patients; median PG diameter was 15 mm (range=4-33 mm). Only 8 lesions (22%) were larger than 20 mm. PG typically only involves the mucosa but can extend into the submucosa and even the full thickness of the luminal wall (13). Histologically, PG is an exophytic, often ulcerated lesion characterized by lobulated proliferation of capillary-resembling vessels in a loose and edematous stroma. The lobules consist of discrete clusters of endothelial cells, and the lumen varies from indistinct to prominent. Therefore, the important differential diagnosis of PG in gastrointestinal tract includes malignant vascular neoplasms such as well differentiated angiosarcoma or Kaposi's sarcoma. Morphologically, these malignant tumors show infiltration, cellular pleomorphism, and nuclear atypia with brisk mitotic figures. Immunohistochemistry and/or polymerase chain reaction for human herpes virus 8 can reliably distinguish pyogenic granuloma from Kaposi's sarcoma.

Due to the surface erosion or ulceration leading to continuous loss of blood in GI tract, PG could be an unrecognized cause of iron deficiency anemia (7, 13). Removal of PGs is necessary in patients with anemia, but post-procedural bleeding is a potential complication (15). Resection is most commonly accomplished by endoscopic mucosal resection, endoscopic polypectomy, or surgical resection. Of these, endoscopic polypectomy was by far the most common treatment method. Regardless of treatment modality, recurrence is rare. Length of follow-up after PG resection was recorded for 19 patients, and only 2 (11%) of these patients had recurrence after resection (13, 16-17). However, the median follow-up in these studies was only 8 months (range=1-39 months).

Conclusion

We report on the first case of PG with CMV infection in the neo-terminal ileum of a patient with Crohn's disease. Gastrointestinal pyogenic granuloma is a rare entity and endoscopists and pathologists should be aware as it can cause GI hemorrhage and lead to anemia. Gastrointestinal PG is a benign reactive lesion and endoscopic resection is considered adequate treatment if the lesion can be completely removed.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

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