Right colon neuroendocrine tumor in a patient with ulcerative colitis: A case study

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Abstract

Neuroendocrine colon tumors are relatively unknown compared with sporadic colorectal cancer; its incidence is low, and it is generally located in the cecum, sigmoid colon, and rectum. The existing relation between neuroendocrine tumors and ulcerative colitis is not frequently described due to the chronic inflammation that leads to neuroendocrine cell differentiation from multipotential cells in the dysplastic epithelium, which can be responsible for colorectal neuroendocrine carcinomas development. The study refers to the case of a patient of 57 years old with ulcerative colitis, abdominal pain, weight loss, and liquid diarrhea with mucus. Physical examination revealed a hardened lesion in the right colonic framework with the tomography of a neoplastic lesion in the ascending colon. When the patient was hospitalized, he developed an intestinal obstruction. A hemicolectomy plus ileostomy procedure was performed resulting in a large cell G3 neuroendocrine tumor in the ascending colon revealed in the biopsy. In this article, the aspects related to the pathophysiology, diagnosis, and treatment of the association of these two pathologies are reviewed in a practical way.

Keywords

Gastrointestinal neuroendocrine tumor, Ulcerative colitis, Inflammatory bowel disease, Neuroendocrine colon tumors.

INTRODUCTION

Gastrointestinal neuroendocrine tumors are rare, derived from neuroendocrine cells, distributed mainly in the mucosa and submucosa of the gastrointestinal tract; their annual frequency is 8.4/100 000 inhabitants, representing 2.5% of gastrointestinal neoplasms and 0.49% of all tumors in general. It predominates between the sixth and seventh decades of life, and the most frequent locations are the cecum, sigmoid colon, and rectum[1].

Neuroendocrine tumors of the colon are relatively rare compared with sporadic colorectal carcinoma, their incidence is very low (0.6%), and there are few reports of neuroendocrine tumors of the colon and rectum in patients with ulcerative colitis. The prevalence of neuroendocrine tumors is difficult to determine, and a definitive relationship between these tumors and inflammatory bowel disease has not been established[2].

CASE PRESENTATION

The patient is a 57-year-old male with a personal pathological history of ulcerative colitis diagnosed 2 years ago with a treatment of mesalazine 3 g every day and a family history of

a brother with ulcerative colitis with a treatment of mesalazine. The patient presented a 2-year onset clinical picture of generalized abdominal pain, weight loss of approximately 20 kg, watery diarrhea with mucus, and abdominal distension. He was admitted to the health center for an exacerbation of his clinical picture 15 days ago with colic abdominal pain accompanied by abdominal distension, watery diarrhea with mucus, and arthralgia without arthritis. In addition, he mentioned a weight loss of 10 Kg in about 1 year.

On physical examination, a suppressive soft abdomen was found and hardening was felt in the flank and right lower quadrant. Admission tests reported hemoglobin 6.0 mg/dL and hematocrit 21.50%; leukocytes 13,300/mm³ with 83.7% neutrophils, platelets 1,257,000, C-reactive protein (CRP) 8.20 mg/dL, albumin 3 mg/dL, total proteins 5.80, normal electrolytes, and kidney function; Non-reactive venereal disease research laboratory (VDRL); vitamin B_{12} > 1000; ferritin 90.30; glomerular sedimentation rate (ESR) 30; serum iron 31; transferrin 205; tumor markers within normal values; tuberculin skin test or negative Mantoux test; serology for cytomegalovirus (CMV), herpes virus, rubella, hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) negative; coproparasitic analysis and *Clostridium difficile* toxin negative for antigen; negative fecal culture and positive occult blood. A 19-point Truelove-Witts index with moderate outbreak was reported.

Abdominal ultrasound reported that an intestinal loop of irregular thickened walls of tumor appearance of 79 x 78 mm was observed at the right flank level with a Doppler ultrasound and increased vascularization. Computed axial tomography (CAT) of the abdomen and pelvis shows diffuse thickening of the walls of the hepatic angle to the ascending colon and cecum with alterations of pericecal fat, and inflammatory changes in the terminal ileum. Therefore, primary injury to the cecum must be ruled out (**Figures 1** and **2**). An upper digestive endoscopic study was performed in which atrophic pangastropathy was observed; Colonoscopy revealed the observation of an alteration of the vascular pattern, erythema, granular, edematous, friable, at the level of the hepatic flexure, and a malignant-looking stenosis that prevents the passage of the equipment with a colonoscopic report of active pancolitis with a score of May 2 for ulcerative colitis. A biopsy of the stenosis and of all the segments was taken; it reported severe inflammatory infiltrate of lymphocytes and plasma cells, neutrophils in the lamina propria, neutrophils in the epithelium, epithelial damage, damage to the surface crypts, cryptitis, cryptic abscess, lymphoid aggregates, superficial and deep ulceration, and loss of some goblet cells suggestive of ulcerative colitis; and in the rest of the segments, no granulomas suggestive of ulcerative colitis were observed.
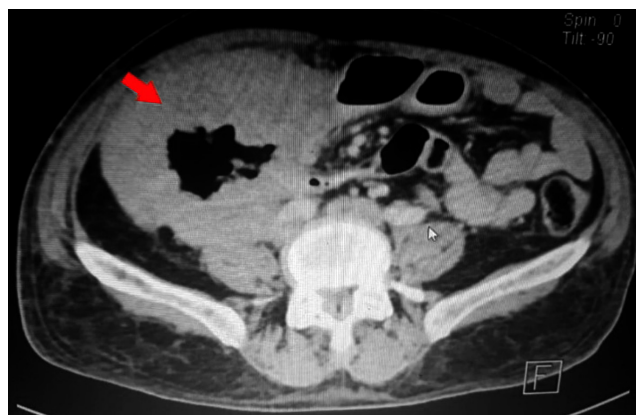
Figure 1. CAT scan of the abdomen in cross section. A thickening of the right colon wall is seen, as seen in the red arrow.

Figure 2. Coronal section CAT of the abdomen in which a thickening of the wall of the right colon is observed with alteration of the pericecal fat, as seen in the red arrow.

Patient with a painful evolution with a Truelove-Witts index of 19 points with moderate outbreak, colonoscopy with a score of May 2, presented moderate to high-intensity abdominal pain on the visual analogue scale (VAS) of 8/10, abdominal distension, postprandial constipation, and vomiting suggestive of intestinal occlusion. An abdominal X-ray was performed in which air-fluid levels were observed at the level of the transverse colon (**Figure 3**).

An evaluation was requested by the coloproctology service, and the surgical procedure was decided in which a
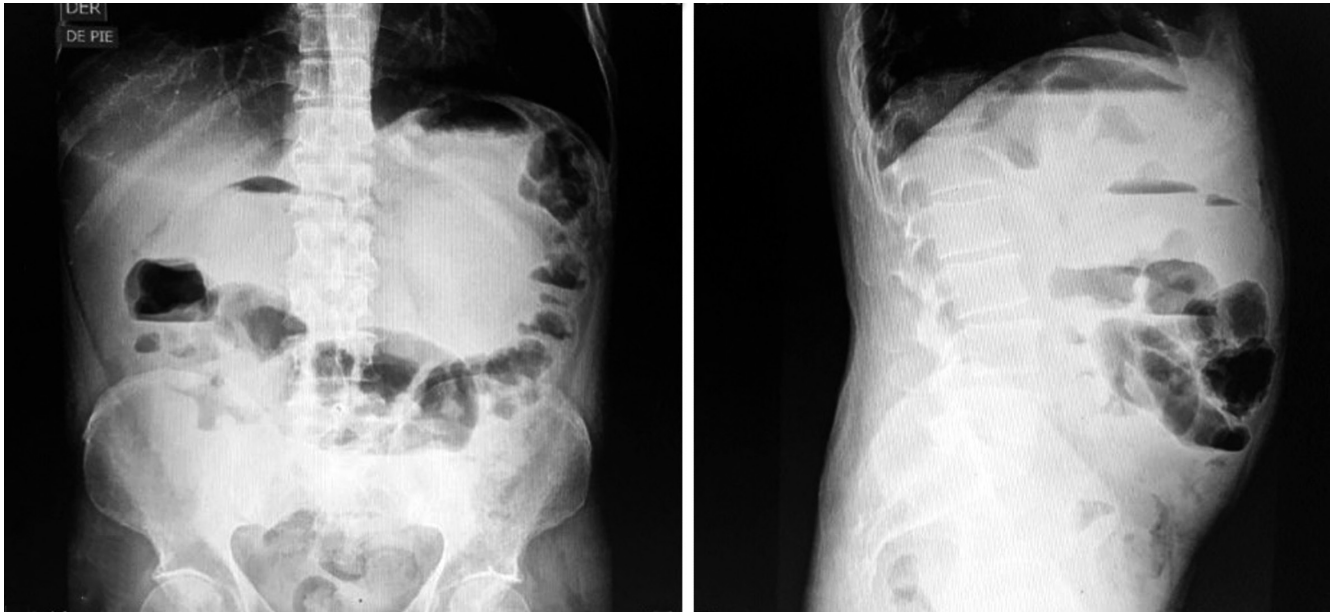
Figure 3. Plain standing abdominal X-ray showing air-fluid levels, suggestive of intestinal obstruction.

total colectomy plus ileostomy was performed with surgical findings of a cecum tumor involving the sigmoid colon and terminal ileum, with a biopsy that reported a total hemicolectomy with Terminal ileum measuring 45 x 4 x 4 cm with a smooth surface covered with a moderate amount of adipose tissue; the cut had elastic consistency. Mucosa with swollen folds and obstructed ileocecal valve were observed at the level of the surgical border. A raised lesion measuring 40 x 30 mm was observed indurated and distant 25 mm from the edge marked with suture. Deformed ascending colon measuring 20 x 8 x 5 cm from the cecum to the surgical margin, with a smooth surface and a purplish-brown color; the cut had elastic consistency. A raised lesion with poorly defined edges was observed at the level of the cecum, 45 cm from the ileal surgical edge and 14 cm from the colonic surgical edge; measured 12 x 10 x 10 cm; it occupied 100% of the intestinal circumference and it obstructed 100% of the colonic lumen, it was 4 cm from the mesenteric surgical border and resulted in a G3 poorly differentiated carcinoma with large cell neuroendocrine features, ulcerated, multicentric, located in 2 foci (cecum and ileum) with a mitotic count of more than 20 mitoses in 10 high-zoom fields. There was no evidence of macroscopic or microscopic transmural perforation, nor evidence of lymphovascular and perineural invasion. There were free ileal and mesenteric colonic surgical margins, with 5 isolated lymph nodes, pericolic free of lesion, and neuroendocrine differentiation immunohistochemistry was not identified.

A multidisciplinary team managed the postoperative period with good evolution, and he was discharged without complications with outpatient controls. The patient did not attend the subsequent consultations nor surgical wound cures, where he presented complications after surgery with infection of the surgical site with inflammatory response syndrome. Then, he was readmitted in poor clinical condition with leukocytosis, neutrophilia, tachycardia, hypotension, and fever with a blood culture of *Staphylococcus epidermidis*, sensitive to clindamycin, linezolid and vancomycin. He went on to intensive care, in which the patient had an unfavorable evolution and died.

DISCUSSION

The incidence of gastrointestinal neuroendocrine tumors is 0.1% and 3.9% of all colorectal neoplasms. In the US National Cancer Institute, only 0.3% of colorectal cancers would be neuroendocrine type, and the Memorial Sloan-Kettering Cancer Center in New York reported an incidence of 0.6% of neuroendocrine carcinomas and only 0.2% are large cell colorectal neuroendocrine carcinoma. They are rare tumors and are rarely described in the context of inflammatory bowel disease in the colon and rectum[3,4].

Carcinoid and neuroendocrine tumors may also be associated with inflammatory bowel disease of the colon depending on the findings of a larger number of neuroendocrine cells in the inflamed mucosa, suggesting that prolonged

inflammation is directly responsible for the development of this disease[5].

Ulcerative colitis has a higher known risk for developing colorectal carcinoma and dysplasia, and the risk increases with the duration and anatomic extent of the disease. A meta-analysis by Eaden et al. in 2001 estimated that the overall prevalence of colorectal cancer in any patient with ulcerative colitis is 3.7%, with a risk of colorectal carcinoma of 2% in 10 years, 8% in 20 years and 18% in 30 years of the disease. Based on this, specific guidelines were established for colorectal carcinoma screening and surveillance in patients with ulcerative colitis to detect neoplasia at a surgically curable stage and to reduce colorectal carcinoma-related mortality[3,6].

Most colorectal carcinomas associated with inflammatory bowel disease are histologically similar to the sporadic type, and tumors with neuroendocrine characteristics are very unusual. Chronic inflammation dysplasia leading to neuroendocrine cell differentiation may be responsible for developing colorectal neuroendocrine carcinomas[7,8].

A study by Sigel et al. reported that neuroendocrine differentiation may evolve from multipotential cells in the dysplastic epithelium, suggesting that long-standing inflammation may be involved in its pathogenesis. For non-carcinoid neuroendocrine tumors, 14 patients with irritable bowel disease (IBD) found that all tumors arose in IBD-affected areas, 8 patients with Crohn's disease, and 6 with ulcerative colitis. 6 of the 14 neoplasms affected the rectum. Neuroendocrine tumors were well differentiated in 11 cases and poorly differentiated in 3 cases; 2 of these 3 patients died at 3 and 11 months after tumor excision[9]. Shigaki et al. observed similar findings in 2013, with 30% to 50% of neoplasms associated with ulcerative colitis showing neuroendocrine differentiation characteristics[10].

The clinicopathological characteristics of these patients are impaired bowel rhythm, chronic diarrhea, hematochezia, obvious dark bleeding, abdominal pain, non-specific symptoms and sometimes obstructive symptoms. Carcinoid syndrome is rare, occurring in less than 5% of cases[11,12].

CAT and magnetic resonance imaging (MRI) have greater sensitivity to establish invasion compromises, but MRI is more sensitive and specific to establish an invasion of the lesion into the *muscularis propria* or suspected lymph node involvement. Currently, positron emission tomography (PET-CT) with gallium 68 (^{68}GA)-Dotatate is considered the image of choice for diagnosing, staging and following-up neuroendocrine tumors, a technique that allows the fusion image and local overexpression of somatostatin receptors to be displayed.

Colon neuroendocrine tumors are rare and aggressive neoplasms characterized by a diffuse organoid growth of tall atypical, small and large neoplastic cells, with more than 20 mitotic figures per 10 high-zoom fields ($\times$ 400), a Ki-67 proliferative index greater than 20%, and large areas of geographic necrosis; neoplastic cells show morphological and immunohistochemical characteristics of neuroendocrine differentiation[13]. It is important to differentiate pathologically neuroendocrine carcinomas from colon and rectal adenocarcinomas because patients may benefit from alternative cytotoxic chemotherapeutic regimens[14].

Differentiation in IBD-related carcinogenesis was demonstrated by Shigaki et al. using immunohistochemistry for p53 and chromogranin A. It was observed that an increase in neuroendocrine cells was present from the early stages of preneoplastic lesions in IBD (low degree of dysplasia), through high-grade dysplasia, until IBD is associated with invasive adenocarcinoma[10].

In the diagnosis of neuroendocrine tumors, only 45% of them are locally limited. Those located in the colon usually present as large tumor masses and, according to a systematic review, they have the worst prognosis; those located in the rectum are diagnosed early in the submucosa, they are polypoid in appearance, and they are covered by glandular mucosa. The least frequent are in the distal colon and rectum; in the 25% of them, the small cell variety predominates, sometimes associated with adenocarcinoma or squamous cell carcinoma. 16% and 40% present distant metastases[1,11].

The recommendations for surgical treatment of neuroendocrine neoplasms of the colon are similar to those for treatment of colon adenocarcinoma: in patients without distant metastases, resection plus local lymphadenectomy (laparoscopy or open) is performed; in tumors with distant metastases, palliative resection plus regional lymphadenectomy, with prior chemotherapy to reduce the lesion. In cases where the resection was not complete, or there was an invasion of adjacent organs, right, left or transverse hemicolectomy, depending on the involvement of lymphatic drainage observed in surgery [15,16].

Treatment of neuroendocrine tumors is completely surgical, and adjuvant treatments, such as chemotherapy or radiation therapy are a minor factor in improving patient survival. Chemotherapy cycles are developed, as is the case with some aggressive regimens, based on the administration of streptozotocin and 5-fluorouracil or of doxorubicin with 5-fluorouracil. Radiation therapy is indicated for bone or central nervous system metastases. Neuroendocrine tumors of the colon and rectum are rare and aggressive with a rapid tendency to locoregional and distant invasion, and surgery is the only effective treatment, although new lines of chemotherapy are being developed[17,18].

Surgical treatment in patients with ulcerative colitis is provided to approximately 20% to 40% of patients at some point in life due to severe impairment in the course of their

disease, and it is indicated as elective in> 90% due to failure of medical treatment, prophylaxis or treatment for high-grade dysplasia, low-grade dysplasia or in association with colorectal cancer, or indicated as emergency in <10% due to perforation, massive hemorrhage, obstruction, and toxic megacolon that does not respond to medical treatment within 72 hours[19].

There is controversy about the management of the rectal stump, and both distal closure using the Hartmann's procedure and the creation of a mucous fistula have been accepted, in which the extrafascial placement of the distal rectosigmoid segment may be associated with fewer septic pelvic complications due to being the closure of the distal stump. Currently, restorative proctocolectomy with ileo-anal reservoir is considered the gold standard for treating ulcerative colitis[20].

Ileorectal anastomosis is often a difficult operation to perform in the background because the ileostomy must be mobilized to bind to the upper end of the rectum. There are also reviews about the complications associated with implementing an ileal reservoir (mechanical, inflammatory, infectious, functional, neoplastic and metabolic)[21].

The preoperative topical use of corticosteroids and mesa-lazine makes it safe to preserve the rectum for ileoproctos-tomy, but it has been shown in studies that the use of daily postoperative topical mesalazine and corticosteroid therapy for an indefinite period performed in the patient's home prevents recurrence of proctitis and results in an acceptable function of ileorectal anastomosis[22].

The most frequent complication is pouchitis, which is especially important due to its high frequency in evolution. Its treatment varies depending on the response and its evolutionary course, which can be managed with a budesonide enema or with mesalazine suppositories to avoid complications of pouchitis. One of the problems of colectomy is the increase of frequency of bowel movements, caused, to a large extent, by the loss of an important function of the colon, such as absorption of water and electrolytes[21].

Palliative measures such as surgery, colostomies, or radiation treatments should be evaluated to improve the patient's quality of life with these tumors[18]. In metastatic diseases, alternative or adjunctive treatments can be used, such as radiofrequency ablation, cryotherapy, and transar-terial chemoembolization[23].

5-year survival ranges from 40% to 70%, depending on the parameters of histological grade, cell proliferation index, and clinical stage; therefore, they correspond to well-differentiated G3 neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas[24].

The tumors are poorly differentiated, extremely aggressive, and have an unfavorable prognosis, with approximately 70% of patients presenting metastatic disease and a reported median survival rate of between 5 and 11 months with one-year survival rates between 10% and 15%[14,25].

CONCLUSIONS

Neuroendocrine tumors associated with ulcerative colitis are relatively rare, and there are few reports of colon neuroendocrine tumors. This is due to chronic inflammation leading to the differentiation of neuroendocrine cells from multipotential cells in the dysplastic epithelium in long-standing patients with Ulcerative colitis, unlike our case, in which the patient had not been diagnosed for many years, which makes us think that more research or reporting of this association is needed. Systematic reviews indicate that large cell and poorly differentiated neuroendocrine tumors have a worse prognosis, with a very low 1-year survival rate.

Conflict of interest

There are no conflicts of interest.

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The authors' own.

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