Intestinal Ganglioneuromatosis: A Manifestation of Type I Neurofibromatosis

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INTRODUCTION

Intestinal ganglioneuromatosis is a rare condition that originates in the enteric nervous system. Histologically, it is composed of Schwann cells, nerve fibers, and ganglion cells. This condition is generally considered benign, with a slow-growing nature and a low likelihood of malignant transformation. [1]

Shekitka and Sobin[2] classified the entity according to the lesion pattern into polypoid ganglioneuroma (PG), a solitary lesion; ganglioneuromatous polyposis (GP), multiple polyps; and diffuse ganglioneuromatosis (DG), exophytic and transmural involvement.

The association of the diffuse form with multiple endocrine neoplasia type 2B (MEN 2B) and neurofibromatosis type 1 (NF1) has been described.[3]

The objective of this paper is to present the clinical case of a young patient with NF1 and a syndrome of abdominal pain and distension caused by cecal DG. The most relevant aspects are discussed, and a review of the literature on this rare entity is provided.

CASE

A 34-year-old female patient presented with a history of weight loss, abdominal distension, digestive intolerance, and recurrent abdominal pain that had persisted for one year. Her medical history included a diagnosis of NF1. The patient exhibited no prior surgical interventions or hereditary predispositions for colorectal cancer or polyposis. An abdominal ultrasound was requested, which revealed no pathological findings. However, a contrast-enhanced abdominal computed tomography scan revealed thickening of the cecum wall (Fig. 1). Colonoscopy revealed a proliferative lesion in the cecum adjacent to the ileocecal valve, occupying 70% of the lumen, and not amenable to endoscopic resection (Fig. 2). The biopsy revealed reactive changes in the colonic mucosa. All laboratory values were within normal limits, including CEA (1.24 ng/ml) and CA 19-9 (3.4 IU/ml).

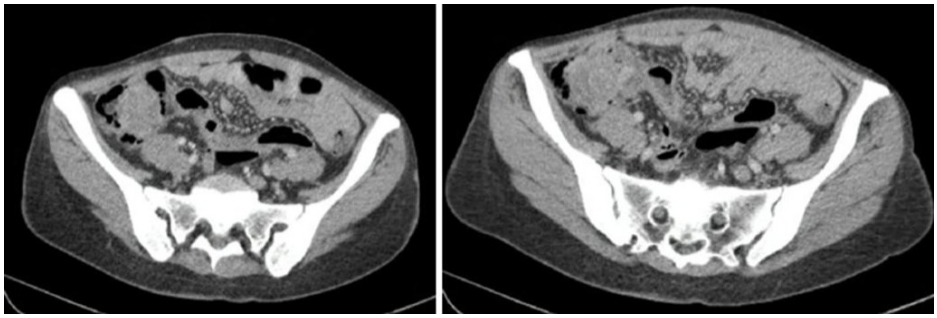

Figure 1. Contrast-enhanced abdominal CT scan showing cecal thickening.

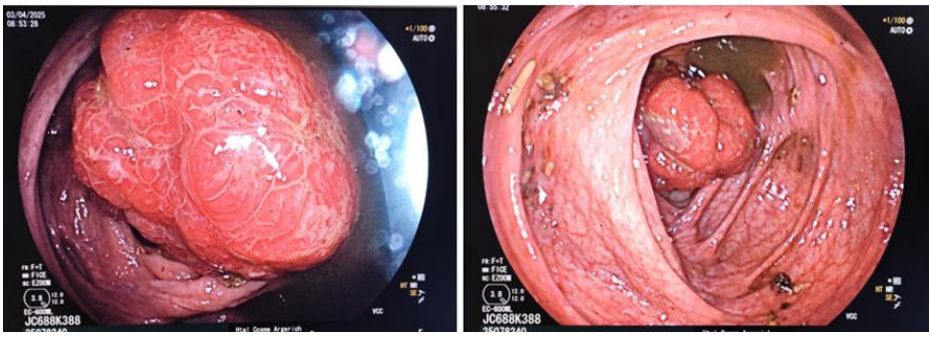

Figure 2*. Colonoscopy. A polypoid lesion occupying a substantial portion of the colonic lumen in proximity to the ileocecal valve is observed.*

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According to the findings, the patient underwent a laparoscopic right colectomy with D2 dissection and intracorporeal stapled side-to-side ileocolic anastomosis.
The pathology report indicated a 5-centimeter villous polypoid lesion with no evident pedicle, occluding 90% of the lumen, and located over the ileocecal valve.
Histopathology revealed a proliferation of neural lineage cells, characterized by spindle-shaped cells, extending from the submucosa to the lamina propria. Fibrous-walled blood vessels and ganglion cells were observed. The mucosa exhibited numerous lymphoid follicles with prominent germinal centers (Fig. 3). Immunohistochemistry revealed positive staining for S100 in spindle cells and synaptophysin in ganglion cells, with focal staining observed in spindle cells.
The morphology and immunophenotype were consistent with a diffuse intramural polypoid ganglioneuroma

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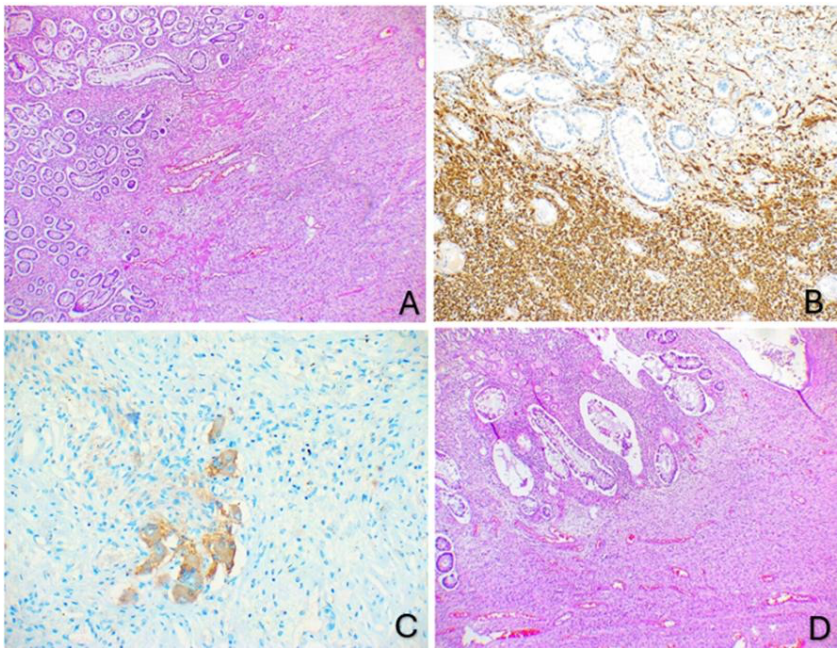

Figure 3. *Histopathology.* ***A.*** *Neural lesion extending from the submucosa to the lamina propria. H&E.* ***B.*** *IHC. Neural marker S100 positive.* ***C.*** *IHC. Synaptophysin positive in ganglion cells.* ***D.*** *Spindle cells with elongated nuclei, arranged in sectors. H&E.*

DISCUSSION

NF1, also known as von Recklinghausen disease, is one of the most common genetic disorders of the neuroectodermal system, with autosomal dominant transmission.[4]
The condition arises from alterations in the NF-1 gene, a tumor suppressor gene located on chromosome 17q11.2, leading to the inactivation of the p21 RAS pathway and the MAP kinase pathway.[5]
Its clinical manifestations are extremely variable and include neoplastic and non-neoplastic disorders that primarily affect tissues of neuroectodermal or mesenchymal origin in different regions, such as the skin, central nervous system, and ocular system.[4]
Up to 25% of patients with NF1 develop neurogenic intestinal tumors.[6] Among these tumors, neurofibromas are the most common; however, abdominal ganglioneuromas are very rare.
As in our patient, most reported cases of ganglioneuromatosis occur in the large intestine, including the rectum.[6] On the other hand, neurofibromas are more prevalent in the small intestine.
The age of presentation is typically between 20 and 50 years, with a median age in the third decade of life.[2]
DG of the gastrointestinal tract is a poorly defined nodular or transmural proliferation of ganglioneuromatotic tissue that diffusely affects the myenteric plexus. Lesions are frequently substantial in size, with dimensions reaching up to approximately 20 cm.[2]

A review by Shekitka and Sobin[2] of 43 patients admitted to the Armed Forces Institute of Pathology in Washington, D.C., for ganglioneuromas of the gastrointestinal tract between 1940 and 1990 established a relationship between the diffuse form of the disease and inherited disorders such as NF1 or MEN 2B. The review revealed that 8 of the 9 patients affected by the diffuse form had one of the aforementioned genetic syndromes.
The incidence of colonic ganglioneuroma in NF1 is unknown, whereas in MEN 2B it approaches 100% and often precedes medullary thyroid carcinoma.[7]
Presentation of symptoms is typically nonspecific, including constipation, diarrhea, vomiting, pain, intestinal obstruction, or gastrointestinal bleeding.[3]
On CT scan, these masses appear as solid, encapsulated, well-circumscribed, hypodense formations that exhibit late enhancemen On MRI, as in other parts of the body, they present as a hypointense mass on T1-weighted images and as a heterogeneous, high-intensity mass on T2-weighted images.[8]
Diagnostic or therapeutic colonoscopies should always be performed, with biopsy or resection of the lesion. Superficial biopsies often fail to provide a diagnosis in cases of deep involvement, as is the present case.
DG is characterized by a proliferation of nerve fibers, ganglion cells, and supporting cells of the enteric nervous system. This proliferation may be poorly defined or diffuse. The growth pattern varies, from hypoplastic spindle-shaped expansions of the

myenteric plexus to transmural ganglioneuromatous proliferations that distort the myenteric plexus and infiltrate the intestinal wall. Immunohistochemical techniques are very useful for confirming the neural origin of the lesion (e.g., antibodies against the S100 protein), and neural differentiation markers (e.g., synaptophysin) are useful for identifying ganglion cells.[2]

Although ganglioneuromas and malignancy may coexist in the gastrointestinal tract, there is currently a lack of evidence supporting a relationship between them.[9] Some authors hypothesize that ganglioneuromas could be considered premalignant, but this hypothesis is primarily based on a few case reports without supporting evidence.[7,10]

In this patient, the symptoms presented prompted further studies that, while not confirming the histological diagnosis, defined the behavior as described in most reports in the literature.

These lesions should be suspected in patients with a previous diagnosis of the aforementioned genetic syndromes. However, in some cases, they may be the first manifestation, requiring a detailed investigation of other associated symptoms and a family history.

CONCLUSIONS

Intestinal ganglioneuromatosis is an extremely rare condition. Its diffuse form is the only one associated with NF1. For diagnosis, a high index of suspicion should be maintained in patients presenting with nonspecific abdominal symptoms or anemia. Treatment options vary depending on the specific symptoms present, although surgical intervention is typically the preferred course of action.

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