CASE REPORT

Intestinal ganglioneuromatosis: an unusual aetiology for occult gastrointestinal bleeding

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SUMMARY

Intestinal ganglioneuromatosis is a rare disorder of the enteric nervous system. It is often associated with neurofibromatosis type 1 and multiple endocrine neoplasia type 2b but, more rarely, it can present in a sporadic and isolated form. A 66-year-old man presented with a 14-year history of iron deficiency anaemia, with no visible bleeding, requiring occasional blood transfusions. Haematological causes of anaemia were thoroughly excluded, and conventional endoscopic and radiological examinations showed no lesions. Capsule enteroscopy identified an ulcerated stenosis in the small bowel, but the biopsies taken at balloon enteroscopy were inconclusive. The patient underwent a laparotomy, which revealed a stiff and ulcerated stenosis in the ileum. Histological analysis demonstrated the presence of diffuse intestinal ganglioneuromatosis. Three years after surgery, the patient is asymptomatic, with normal haemoglobin levels. This case demonstrates an isolated form of intestinal ganglioneuromatosis, with an atypical presentation, difficult to diagnose despite an exhaustive evaluation.

BACKGROUND

Intestinal ganglioneuromatosis (IGNM) is a rare neoplastic condition characterised by marked proliferation of ganglion cells, Schwann cells and nerve fibres in the wall of the bowel.¹ It is generally described in children, in association with multiple endocrine neoplasia (MEN) type 2b and neurofibromatosis type 1 (NF1). IGNM is a rare condition in adults, particularly in a sporadic and isolated form.² Its clinical expression is variable, leading to different designations in the literature. The polypoid form of ganglioneuromatosis can be solitary, where patients have single colonic polyps composed of spindle and ganglion cells; or multiple, most commonly in the terminal ileum and colon, also known as ganglioneuromatous polypoidosis. The diffuse form is characterised by hyperplasia of the myenteric plexus and transmural proliferation of ganglioneuromatous tissue in the bowel wall.³ This condition may affect any segment of the gastrointestinal tract, but the ileum, colon and appendix are most frequently involved.⁴ The clinical presentation is variable, and depends on the location and extent of the lesion as well as its effect on intestinal motility. The most frequent symptoms are changes in bowel habits, abdominal pain and occlusive episodes due to stricture formation, but patients may remain asymptomatic for decades.⁵ Occult haemorrhage and iron deficiency anaemia secondary to ulceration of the intestinal mucosa are

rare complications of IGNM, making the diagnostic process very challenging.⁶

CASE PRESENTATION

We present a case of a 66-year-old man, an electrician, diagnosed with iron deficiency anaemia of 14 years' duration. The patient was referred to gastroenterology department in 2006, after 8 years of investigation in the haematology department. The anaemia was found in blood analysis requested to investigate symptoms of fatigue, but the patient had no other clinical manifestations, such as abdominal pain, changes in bowel habits (diarrhoea or constipation), visible blood loss (haematemesis, melena, haematochezia, haematuria), fever or weight loss, during all the years of follow-up. He also denied unregistered utilisation of antiplatelet, anticoagulant or anti-inflammatory drugs, had no history of alcohol or tobacco consumption, and followed a varied and complete diet. The patient's additional medical history included cholecystectomy and amygdectomy many decades ago, and chronic atrial fibrillation treated with propafenone. He was also taking omeprazole on a daily basis and regular infusions of intravenous iron. Regarding his family history, there were no other cases of anaemia, inflammatory bowel diseases or gastrointestinal tumours. Physical examination was normal. Apart from the intermittent asthenia, coincident with recurrent worsening of haemoglobin (Hb) values, the patient had no other symptoms.

INVESTIGATIONS

Initial investigation was made in the haematology department in order to exclude haematological causes of anaemia and the most frequent causes of gastrointestinal occult haemorrhage. The analytical study showed no changes apart from hypochromic microcytic anaemia (table 1) with ferritin and transferrin saturation between 10–54 ng/mL and 17–30%, respectively, despite regular therapy with intravenous iron. All other analytical studies were normal, including reticulocyte count, coagulation, biochemical parameters (renal function, hepatic parameters, lactate dehydrogenase, C reactive protein), urine analysis, thyroid function, immunoglobulins, protein electrophoresis, tumour markers (CEA, CA19.9, PSA; AFP, β_2 microglobulin), cobalamin and folic acid. The autoimmune study was also negative, including coeliac disease antibodies (anti-transglutaminase, endomysial, gliadin), antinuclear and Extractable Nuclear Antigens (ENA) antibodies, antidouble-stranded DNA (dsDNA), antineutrophil cytoplasmic antibody and

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Table 1 Evolution of the haemoglobin (Hb) and mean corpuscular volume (MCV) values before surgery

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Hb (g/dL)	8.9	12.5	10.4	10.7	10.9	8.8	10.4	13	9.4	10.7	6.9
MCV (fL)	76	90	81	78	88	82	85	94	85	85	67

anti-*Saccharomyces cerevisiae* antibody. Faecal occult blood tests were performed on different occasions, and were positive only in the first sample.

In the year 2000, the patient had undergone an upper gastro-intestinal endoscopy with duodenal biopsies and ileocolonoscopy. These examinations showed no significant alterations, thus excluding atrophic gastritis, *Helicobacter pylori* gastritis, coeliac, Whipple's or apparent inflammatory bowel diseases. The genetic study found no mutations in the Tmprss6 and ferroportin genes, and hereditary haemoglobinopathies were also excluded. In 2006, the patient had been referred to the gastroenterology department for further investigation. At that time, he had a repeat standard endoscopic study, which was again normal, and underwent a CT enteroclysis, and abdominal and pelvic CT scan, which showed no changes and ruled out the presence of intestinal tumours. In 2010, due to another fall in the Hb level, a capsule enteroscopy was performed, and identified an ulcerated stenosis in the small bowel that caused temporary retention of the capsule (figure 1). To clarify the lesion, a double balloon enteroscopy was performed, and biopsies were taken from a small jejunal ulcer (figure 2). The histological results showed no significant alterations. In 2012, the patient presented a minimum Hb of 6.9 g/dL with mean corpuscular volume of 67 fL, requiring blood transfusion. It was then decided to carry out an intraoperative enteroscopy, which led to resection of an ileum segment, which presented a stiff and ulcerated stenosis (figure 3), associated with fat densification and mesenteric lymphadenopathy. Macroscopically, there was an ileum segment 19 cm in length, with an ulcerated lesion of 3.5×2 cm, surrounded by regular margins, conditioning stenosis and rigidity of the wall. The remaining intestinal wall had no changes on macroscopic study.

In the histological analysis, the lesion aforementioned corresponded to diffuse infiltration of the submucosa by nerve fibres

and ganglion cells that was so exuberant, it led to ulceration of the mucosa and reached the muscular layer. The immunohistochemical study showed intense and diffuse expression for S100 protein and NSE (neuron-specific enolase). The remaining mucosa had no changes or evidence of tumour. The four isolated ganglia presented reactive follicular hyperplasia and fibrotic areas. This description was compatible with diffuse IGNM (figures 4–6).

TREATMENT

The patient was submitted to explorative laparotomy and intestinal resection. No further therapies were necessary.

OUTCOME AND FOLLOW-UP

Three years after surgery, the patient is asymptomatic, with stable Hb (13.6 g/dL), and no need of intravenous iron or blood transfusions. The association of IGNM with systemic syndromes, namely MEN type 2b and NF1, was excluded by careful physical examination, which ruled out dermal neurofibromas, café-au-lait macules, Lisch nodules and marfanoid habitus; thyroid and abdominal ultrasonography was also performed, with no evidence of adrenal or thyroid tumours.

The patient maintains follow-up with routine analysis and abdominal ultrasonography.

DISCUSSION

Neurofibromatous lesions of the gastrointestinal tract include hamartomatous benign lesions, characterised by marked proliferation of nerve fibres and ganglion cells of the enteric nervous system. These lesions are more frequently seen in children, in association with systemic syndromes, namely MEN 2b (pheochromocytoma, medullary thyroid cancer, mucosal neuromas)

Figure 1 Capsule enteroscopy image revealing an ulcerated stenosis in the small bowel—probably in the distal jejunum or proximal ileum.

Figure 2 Small jejunal ulcer found on double balloon enteroscopy.

Figure 3 Surgical specimen of an ileum segment that presented a stiff and ulcerated stenosis.

and NF1 (café-au-lait spots and axillary freckling, skeletal dysplasias, and benign and malignant nervous system tumours, most notably benign neurofibromas). An association with Cowden syndrome has also been reported.² Gastrointestinal involvement can be the first manifestation of these syndromes. Its occurrence in the absence of other clinical features of NF1 and MEN 2b is extremely rare,⁷ and, as in our case, the definitive diagnosis is very difficult and scrupulous postoperative follow-up is necessary to exclude the possible association with NF1 and the onset of local recurrences.⁶ Besides IGNM, our patient had no other clinical diagnostic criteria to suggest the syndromes aforementioned, so a genetic test was not performed.

This rare condition can present in a polypoid form, with solitary or multiple polyps, or with a diffuse and transmural appearance. Diffuse IGNM most commonly involves the colon, appendix and terminal ileum,³ as was the case in our patient, in whom the lesion affected an ileal segment. The clinical, radiographic and histological findings of ganglioneuromatous lesions are not specific to NF1 or MEN 2b, and identical features have been reported as an isolated finding in patients with no evidence of systemic disease.^{2 6 8 9} This was the case with our patient. Chambonnière *et al*² reported a series of adults with IGNM and showed that, in adulthood, the diagnosis is not suggested by the clinical presentation but is established at the pathological examination. This is particularly true in cases with atypical symptoms. The clinical presentation of ganglioneuromatous lesions that affect the gastrointestinal tract depends on the location of the lesions, and on whether they are focal or diffuse, their size, their effect on gastrointestinal motility and on their possible impingement on adjacent structures. The most common symptoms are changes in bowel habits, diarrhoea or constipation, abdominal pain, intestinal obstruction and palpable abdominal masses.^{2 10-13} There are other rarer complications such as ulcer of the intestinal mucosa,

intestinal haemorrhage, perforations, steatorrhoea, pancreatitis and obstructive jaundice.^{5 14} Looking at the presenting features of our case, we can see that this patient was, apart from the asthenia related to the anaemia, asymptomatic. To the best of our knowledge, this is the first case of IGNM manifested exclusively by recurrent iron deficiency anaemia.

The size of the lesions is variable, ranging from millimetres to masses of 17 cm, and mimicking a malignant stenosis. In diffuse forms, a CT scan can reveal this circumferential narrowing and thickening of the affected intestinal loops, and in some cases with ileal involvement, the comb sign may be present, simulating Crohn's disease.^{10 15} In the present case, the radiological examinations (CT enteroclysis and abdominal and pelvic CT scan) did not identify any relevant changes. Even though these examinations were performed 4 years before the capsule endoscopy revealed an ulcerated stenosis, we can speculate that, at that time, the lesion was already present, and should have been seen on CT enteroclysis, and that in this case it was a false negative of the radiological method; another possibility is that the lesion could have been significantly smaller and an insufficient distension of the ileal loops did not allow its detection. Similar to what happens in radiological methods, the endoscopic appearance of IGNM depends on the focal or diffuse nature of the lesions. As the lesions arise deep in the epithelium, they manifest as single or multiple subepithelial masses of variable size and distribution.⁹ However, changes in the innervation of the intestinal wall due to hyperplasia of the myenteric plexus and other structures of the autonomic nervous system, determine segmental changes of intestinal contraction, leading to a tubular aspect of the lumen.² Ulceration due to erosion of the epithelium over the surface of lesions has been described, particularly in large solitary lesions.⁹ Similar to our case, IGNM

Figure 4 Diffuse infiltration of the submucosa by nerve fibres and ganglion cells that is so exuberant, it causes ulceration of the mucosa and reaches the muscular layer (H&E ×100).

Figure 5 Proliferation of nerve fibres and ganglion cells (H&E ×200).

Figure 6 Immunohistochemical study showing intense and diffuse expression for neuron-specific enolase (NSE) (×200).

can appear as an ulcerated stenosis, and some differential diagnoses should be ruled out, namely Crohn's disease, cytomegalovirus infection, intestinal tuberculosis, intestinal tumours (gastrointestinal stromal tumour, lymphoma, adenocarcinoma), chronic ischaemia, NSAIDs enteropathy and amyloidosis. The clinical presentation and long-term evolution of this particular case were not suggestive of a malignant cause, but considering the unspecific endoscopic findings, the absence of radiological changes and the low incidence of IGNM, the definite diagnosis was almost impossible without histological confirmation. Endoscopic biopsies are the mainstay of diagnosis, but when used in an attempt to sample deep-seated lesions, the biopsies may yield only unaffected overlying bowel mucosa or minimally diagnostic superficial lesional tissue.⁹ In the current case, there were many doubts as to whether the jejunal ulcer biopsied in the double balloon enteroscopy corresponded to the ulcerated stenosis revealed in the capsule endoscopy, because the size and consequent narrowing of the lumen were not equivalent. In fact, the ileal location of the lesion found in the laparotomy confirmed that, probably, the biopsies were not taken from the required lesion. So we cannot be sure if endoscopic biopsies would be sufficient to obtain the correct diagnosis.

Taking into account the diagnostic doubts and recurrent character of the anaemia, with Hb levels requiring blood transfusions and regular intravenous iron infusions, the decision to perform an explorative laparotomy seems justified. In fact, this was the key for the definite diagnosis because the surgeons were able to identify the ileal segment with a stiff stenosis, and the resected specimen allowed a complete pathological examination. The characteristic proliferation of nerve fibres and ganglion cells determines a fusiform hyperplastic expansion of the myenteric plexus or even a transmural ganglioneuromatous proliferation that distorts the myenteric plexus and infiltrates the adjacent bowel wall. Immunohistochemistry provides a precious aid in the diagnosis. The immunoreactivity of ganglion cells to S100 protein, glial fibrillar acidic protein, vimentin, NSE and synaptophysin confirms the nervous origin of the cell proliferation.²

The relationship between IGNM and malignancy is not consistently established. However, the coexistence of IGNM with adenocarcinoma of the small bowel and colon has been reported in some occasions.^{2 16–21} A fact to emphasise is that most of

these cases were not associated with NF1. This association with intestinal adenocarcinoma generates uncertainty regarding the therapeutic management of these situations. In cases of diffuse IGNM limited to a short digestive segment, as in our patient, the treatment of choice is surgical resection, particularly in cases of stenosis or changes in gastrointestinal motility that result in sub-occlusive symptoms. In our case, the stenosis was not symptomatic but the recurrent anaemia reached significantly lower values, which justified a more aggressive diagnostic and therapeutic approach. This should also be considered whenever a neoplastic lesion is suspected. In cases of diffuse involvement of the small bowel requiring extensive resections with inherent risk of short bowel syndrome, the decision to operate is more difficult.

Regarding the scarcity of cases reported in the literature and the potential, although rare, of neoplastic degeneration, there are many doubts as to the best follow-up strategy, namely, the type of examination to make and the time intervals to adopt. In cases such as ours, we should question whether it is necessary to perform regular non-invasive surveillance of the small bowel (with capsule endoscopy and/or magnetic resonance enteroclysis) or whether to wait for symptoms to develop so as to justify investigation.

Learning points

- Diffuse intestinal ganglioneuromatosis (IGNM) is a rare condition, particularly in adult patients, in the absence of systemic syndromes (NF1, MEN 2b).
- The clinical presentation of IGNM is very variable and the patient can be oligosymptomatic, with atypical presentation, namely, isolated anaemia.
- This diagnosis should be considered when the most frequent causes of iron deficiency anaemia have been excluded.
- The diagnostic work up is challenging and the definite diagnosis is only possible after resection and pathological analysis of the involved segment.
- The optimal therapeutic strategy is surgery for symptomatic lesions or with suspected malignancy, but the best follow-up protocol has not been defined.

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