Gangliocytic Paraganglioma: a Rare Cause of Gastrointestinal Bleeding

Alina Boeriu¹, Daniela Dobru¹, Rareș Georgescu², Simona Mocan³, Cristian Boeriu⁴

ABSTRACT

Duodenal neuroendocrine tumors (NETs) are rare tumors, consisting of five different types of tumors. In many cases, they may be asymptomatic, leading to delay in diagnosis. Clinical symptoms are related to local tumor growth and mucosal ulceration. We report a 38-year-old man with duodenal gangliocytic paraganglioma causing overt upper gastrointestinal bleeding and anemia. We describe specific clinical and histopathological features of the tumor, and review the diagnostic and therapeutic strategy. Gangliocytic paragangliomas are regarded as benign tumors. However, the disease recurrence and the malignant potential of the tumor have also been reported.

Key words: gangliocytic paraganglioma – immunostaining – surgical excision – metastasis.

INTRODUCTION

Gastrointestinal neuroendocrine tumors (NETs), also called carcinoids, arise from cells of neuroendocrine systems, and were first described as a distinct class of malignant tumors with less aggressive behavior than adenocarcinomas of the gastrointestinal tract [1]. Morphologically, carcinoids are identified by positive staining for neuroendocrine markers such as chromogranin A, synaptophysin, Leu7, and neuron-specific enolase (NSE). Duodenal NETs are rare tumors, representing about 4% from all gastrointestinal carcinoids [2]. Different types of neuroendocrine tumors have been described in the duodenum, consisting of gastrinomas, somatostatinomas, non-functional NETs, gangliocytic paragangliomas and poorly differentiated NETs [3].

CASE REPORT

A 38-year old man was referred to our department with melena. He had a previous history of mild anemia (hemoglobin 10.7 g/dl), intermittent hematochezia, and fatigue in the past year. A colonoscopy performed for the evaluation of anemia and rectal bleeding revealed hemorrhoids. At admission to our hospital, physical examination showed pallor, tachycardia and hypotension. Laboratory values revealed severe anemia and iron deficiency (hemoglobin 5.2 g/dl, hematocrit 18%, serum iron 20 μg/dl). After hemodynamic resuscitation, the patient underwent an esophagogastroduodenoscopy. On endoscopy, a submucosal ulcerated tumor with active bleeding was detected in the second part of the duodenum (Fig. 1). Biopsy specimens from the lesion showed normal duodenal mucosa. A CT scan of the abdomen was performed and no local lymph node involvement was identified. The patient underwent local surgical excision.

The histopathological examination of the resected specimen evidenced a gangliocytic paraganglioma, 15 mm in size, located in the submucosa (Fig. 2), consisting of three components: predominant spindle cells (Schwann cells) forming small fascicles, large epithelial (endocrine) cells in nests and pseudo-glandular structure and large ganglion cells scattered singly and in small clusters (Fig. 3). Immunostaining examinations showed positivity of spindle cells for S-100, while the endocrine cells were positive for chromogranin A (Fig. 4).
The patient was discharged with normal levels of hemoglobin and hematocrit. One year following surgical resection, he showed no endoscopic or imaging evidence of tumor recurrence, and normal laboratory parameters.

**DISCUSSION**

Gangliocytic paraganglioma was first described by Dahl et al. in 1957 [4]. The tumor is usually detected in the sixth decade of life [5]. Patient ages range from 15 years to 82 years, with male predominance [6]. Gangliocytic paragangliomas account for 6% to 9% of duodenal NETs and represent the third most frequent histopathologic type after gastrinomas and somatostatinomas [3]. They are considered benign hamartomatous tumors, derived from the ventral pancreatic primordium [2, 7].

The duodenum and periampullary region represent the most common sites of occurrence (90%) [6], but the tumor has also been described in other anatomic locations: esophagus, stomach, jejunum, appendix, pancreas, spinal cord, nasopharynx, and the lung [8-15]. The diagnosis may be often delayed because of the small size of tumors, most of them being asymptomatic or showing nonspecific symptoms, such as vague abdominal discomfort or dyspepsia. In many cases, gangliocytic paraganglioma represents an incidental endoscopic finding, when a polypoid submucosal mass is detected mainly in the first or the second part of the duodenum. Due to the submucosal location of the tumor, the reported diagnostic rate by biopsy before surgical intervention is low (11.4%) [6]. Barium studies of the upper gastrointestinal tract reveal an intraluminal filling defect [5].

Clinical symptoms include intestinal obstruction, biliary obstruction, overt gastrointestinal bleeding and anemia, related to local tumor growth and mucosal ulceration [16]. In a literature survey performed by Okubo et al., gastrointestinal bleeding was reported to be the most common symptom, followed by abdominal pain and anemia [6]. Although in most cases the tumors are endocrinologically silent, rare situations have been described when the tumor synthesizes somatostatin leading to diarrhea and steatorrhea [17].

Histologically, the tumor is composed of epithelioid endocrine cells, ganglion cells and spindled Schwann-like cells, intermingled with the smooth muscle and small pancreatic duct, especially in tumors located in the ampullary region, producing a very complex lesion [18]. The components are
identified by using specific immunohistochemical markers. Spindle cells stain positive for S-100 protein, neuron-specific enolase (NSE) and synaptophysin. Ganglion cells are positive for synaptophysin, neuron-specific enolase, somatostatin and pancreatic polypeptide (PP). Endocrine cells show positive staining for neuron-specific enolase, synaptophysin, pancreatic polypeptide, somatostatin, chromogranin A, cytokeratins and serotonin [6].

Radical surgical excision or endoscopic resection of the tumor represent available therapeutic alternatives [5, 19]. A previous evaluation by imaging studies is necessary for determining endoscopic resectability. Local lymph nodes metastasis should be excluded before endoscopic treatment. Endoscopic ultrasonography (EUS) evaluates the depth of tumor invasion and local lymph node metastases [20]. The tumor is mainly located within the submucosal layer, but in some cases it may involve the muscularis propria and even the mesentery [17]. Computed tomography (CT) and magnetic resonance imaging can be used to evaluate metastatic spread of the tumor [2].

Gangliocytic paragangliomas are usually benign, in contrast with gastrin-cell or somatostatin-cell tumors arising in the same areas. Occasionally, a large tumor (over 2 cm) may spread to local lymph nodes, mainly due to the endocrine component of the tumor. A tumor exceeding the submucosal layer represents a risk factor for lymph nodes metastases [6]. The recurrence of a tumor after therapeutic procedures has been reported [16, 21, 22]. Specific histologic features to predict malignant potential have not been yet defined. Therefore, pancreaticoduodenectomy with lymph node dissection has been proposed as a better option in large tumors with nuclear pleomorphism, mitotic activity, and infiltrative margins [16].

Liver and lymph nodes metastases have been reported in a patient presenting a small (1 cm in diameter), non-infiltrative gangliocytic paraganglioma, with Ki-67 proliferation index less than 1% [24]. Criteria for predicting the risk of metastasis are still under evaluation [18]. Immunohistochemical evaluation using Ki-67 seems to have a limited value as a prognostic indicator, as well as bcl-2 and p53 [6]. However, based on published data, patients with gangliocytic paragangliomas have a good prognosis, even in the presence of lymph nodes or liver metastasis [6, 23].

The difficulty in predicting the behavior of the tumor warrants an accurate evaluation by imaging studies, prior to therapeutic intervention, as well as a long-term follow-up. In our patient with gangliocytic paraganglioma confined to the submucosa neither tumor recurrence nor metastasis have been detected over a one-year follow-up period.

**CONCLUSION**

Clinical presentation of patients with duodenal gangliocytic paraganglioma may be asymptomatic until the mucosal ulceration causes an overt gastrointestinal bleeding. The tumor may be associated with signs of obstruction (intestinal or biliary), depending on its size and the proximity to the ampulla of Vater. Imaging studies help to make the therapeutic decision. The tumor can be cured by surgical or endoscopic treatment, although lymph nodes and liver metastasis, as well as the recurrence after incomplete excision have been reported. Due to the possible aggressive behaviour and the lack of predictive markers for progression of the tumor, close surveillance is advised.

**Conflicts of interest:** Nothing to declare.

**Authors’ contributions:** A.B. performed the endoscopic examinations and wrote the manuscript. R.G. performed the surgical resection and the literature search. S.M. performed the histopathological examination. C.B. and D.D. critically reviewed the manuscript. All authors approved the final manuscript.

**REFERENCES**