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Surgical treatment of gastrointestinal autonomic nerve tumors (GANT) in children-2 case reports

Case Report

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Abstract: Gastrointestinal autonomic nerve tumors form an uncommon subcategory of stromal tumors of the intestinal tract although their histologic appearance is similar to other gastrointestinal stromal tumors. Our aim was to evaluate our experience in the diagnosis and therapy of these kinds of tumors. Two patients were admitted to the Pediatric Surgery Clinic in Niš with abdominal pain and a palpable mass in the abdomen. After excision, the tumor tissue was sampled, sent for histopathological diagnosis, and examined by light microscopy, immunohistochemistry, and electron microscopy. Postoperatively, both patients recovered without complications. The patient with the tumor bulk in the mesentery of the small bowel had no evidence of tumor progression 6 years after surgery. In the second case, a giant tumor was present along the greater curvature of gaster. Even with a tumor of this size, there were no signs of progression 10 years after surgery. Radical surgical resection of gastrointestinal autonomic nerve tumors seems to be the curative approach to date, and long-term survival is possible even with large tumors.

Keywords: *Autonomic nerve tumor • Immunohistochemistry • Children*

1. Introduction

Gastrointestinal autonomic nerve tumors (GANT) are extremely rare and have been defined as a new subcategory in the group of gastrointestinal stromal tumors. GANT originate from intestinal autonomic nervous structures (the Meissner and Auerbach plexus, plexus subserosus, and deep muscle plexus). The cellular origin of the tumor has not been definitely documented, but it is considered to correspond with immature ganglion cells, the interstitial cells of Cajal, that are intestinal pacemaker cells [1].

GANT is currently defined as a type of gastrointestinal-tract mesenchymal tumor containing spindle cells (less commonly, epitheloid cells or, rarely, both) and showing CD 117 (c-kit protein) positivity in more than 95% of cases. Herrera et al. first described this tumor in 1984 as a plexosarcoma [1-2], and the total number of cases in the literature is 43.

Histologically, they are mostly low-grade tumors. They are varied in their clinical, histopathologic, and genetic features. It is believed that they are caused by the mutation of c-kit genes. Definitive confirmation and diagnosis of GANT relies mainly on precise electron microscopical and immunohistochemical examination [3]. Histologic and immunohistochemical markers for differentiation of GANT from other mesenchymal tumors are scenoidal corpuscles and expression of CD117, CD34 antigen, or both.

Adequate radical resection is followed by a good prognosis and a high rate of five-year survival.

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Figure 1. GANT in the mesentery of small bowel.

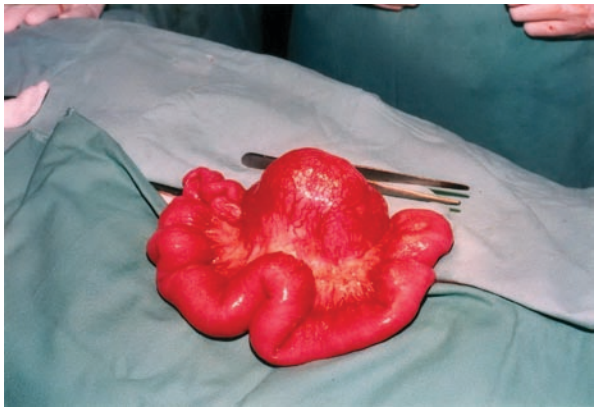
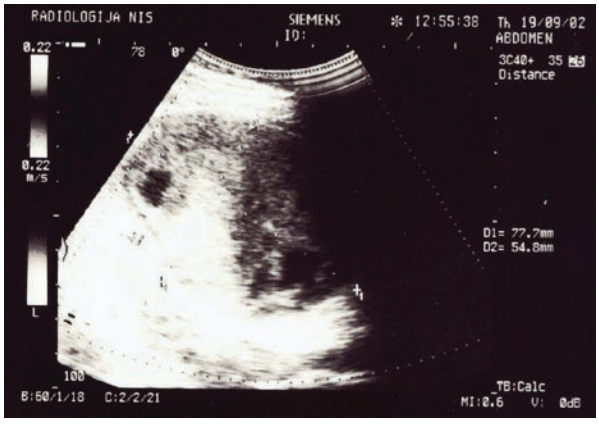


Figure 3. Abdominal ultrasound revealed a large, nonhomogeneous solid mass with multiple cysts in the left paraovarian space.



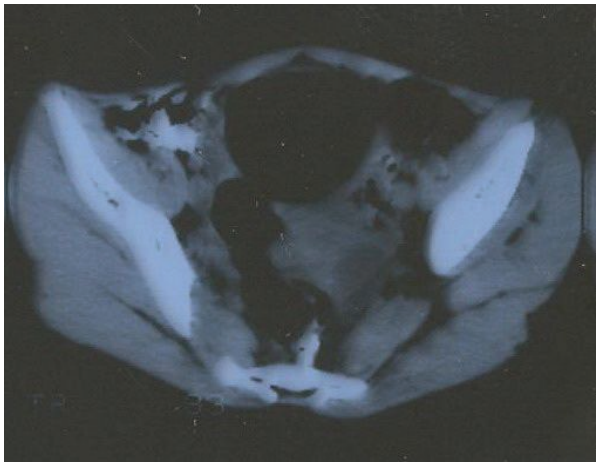
2. Case 1

A 9-year-old girl presented with pallor and intermittent, severe abdominal pain of 3 months' duration followed by anorexia. Physical examination was notable for a palpable tumor mass in the left side of the abdomen. A radiograph of the abdomen taken with the patient upright revealed incipient air-fluid levels.

Abdominal ultrasound revealed a large, nonhomogeneous solid mass with multiple cysts in the left paraovarian space (Figure 1). Parasagitally, a CT scan showed an oval-shaped, encapsulated cyst (80 x 56 mm) in the hypogastrium in front of the left kidney, extending caudally to the urinary bladder (Figure 2). The initial clinical diagnosis was: ***Mesenchymal tumor of small bowel.***

A median laparotomy was performed, and the peritoneum was opened The tumor bulk was localized to the mesentery of the small intestine (Figure 3). The tumor was excised completely, with resection of the bowel and

Figure 2. CT scan showed a tumor mass in the mesentery of the intestine.



mesentery where the changes were found initially. A termino-terminal (TT) anastomosis and appendectomy were subsequently performed.

Specimens were obtained intraoperatively and sent for histopathological analysis. Resected tissue was preserved in fresh condition. At the same time, the specimens were photographed and the dimensions of tumor tissue recorded. The tumor was well vascularised, with a capsule in the mesentery; the weight was approximately 200 g, and it measured 7 cm by 5 cm, with no infiltration of the intestinal wall, but partly with central fields of hemorrhage. The surrounding tissue and regional lymph nodes showed no change. Microscopical examination detected tumor spindle-star cells with low and middle cellularity.

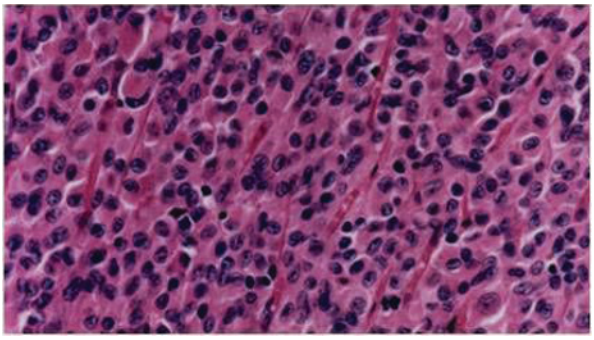
The mitotic index was very low (<5/50 HPF). The tumor was positive for CD117 (c-kit), CD34, vimentin, neurofilaments (NFP), neuron-specific enolase (NSE), and S-100 protein. The histopathologic diagnosis was: ***Gantoma myxoides mesenterii.***

No further treatment was rendered. The patient has been followed with serial computed tomography (CT) scans and has had no recurrence 6 years after the diagnosis was made.

3. Case 2

A boy aged 12 years was admitted to our hospital in a state of severe hemorrhagic shock and deterioration. Ten days before admission, he had abdominal pain below the right costal arch and vomiting. His hemoglobin was 5.8 g per deciliter. Urgent surgical exploration was peformed without a diagnosis by previous ultrasound study and CT.

Figure 4. An epithelioid pattern with increased mitotic activity is shown (H & E, original magnification.



The abdomen was opened via a pararectal and subcostal laparatomy, and a large amount of blood from necrotic tumor bulk was released from the peritoneum. The tumor was 10 by 8 cm in size; it is in the region of the lower and middle third of the greater curvature of the stomach and extended to the pylorus; it was covered by the greater omentum and was attached by a short pedicle to the gastric wall.

Radical excision of the tumor followed, with no need for partial gastrectomy, because the tumor was on a pedicle.

Specimens were obtained intraoperatively and sent for histopathologic analysis. The tumor measured 10 by 8.5 by 3.5 cm, with no infiltration of the capsule. No changes were found in the peritoneum or in other intra-abdominal organs, and there were no enlarged lymph nodes. The mitotic index was very low (<5/50 HPF) (Figure 4). The tumor was positive for CD117 (c-kit), CD34, vimentin, neurofilaments (NFP), neuron specific enolase (NSE), and S-100 protein. Histopathologic examination revealed a GANT: ***gantoma myxoides mesenterii-low grade***.

No further treatment was rendered. The patient has been followed with serial MRI scans every 6 months and currently has no evidence of recurrence 10 years after surgery.

4. Methods

The tumor tissue was photographed and measured. Then, 1-mm^3 tissue clips were fixed in 10% neutral paraffin, cut at a thickness of 3 μm, and stained with hematoxylin and eosin for analysis. Immunocytochemical studies were carried out on selected formalin-fixed, paraffin-embedded tissue sections with use of neuron-specific enolase (NSE), vimentin, smooth muscle actin (SMA), desmin, neurofilaments (NFP), CD 34 CD 117 and S100 protein.

5. Discussion

GANT is a subcategory of gastrointestinal stromal tumors. The first case was described by the Herrera in 1984 [1], and the total number of cases in the literature is very small.

The clinical presentation of GANT varies widely and depends on tumor size and location. The type of GANT that causes symptoms tends to be larger than 5 cm in diameter. Symptoms are most commonly related to mass effect or bleeding. Anemia is the common thread in most of the cases. The presence of gastric ulceration has no importance in determining the biological potential, although may be related to tumor size. The most common localization of tumors is in the stomach (12 cases), small intestine (20 cases) [4], and esophagus (2 cases), but they may extend along the entire intestinal tract, even into the retroperitoneal space (3 cases), mesentery (3 cases), bladder (2 cases) [5], colon [6,7], and rectum [8]. The literature to date supports an age range of 10 to 85 years, with a median age of 61 years. It also demonstrates a near equal male-to-female incidence [9].

Despite the small number of reported cases in the literature, it seems that gastric tumor localization predominates in the pediatric population, affecting slightly more females than males and those in the second decade of life. In older patients, intestinal localization predominates.

These tumors are characterized by ultrastructural features resembling enteric autonomic-nerve cells, without epithelial, Schwannian, or smooth-muscle differentiation, showing CD 117 (c-kit protein) positivity in more than 95% and CD 34 positivity in more than 50% of cases [12]. GANT typically show immunoreactivity with neural markers, such as neuron-specific enolase, and possess features of a nerve plexus, with dense-core neurosecretory granules and synapse-like clefts [13].

All GANT with <5/50 high-power field (HPF) are considered to be benign lesions with low malignant potential. Tumors with mitotic division that ranges from 5 to 50 are classified as malignant. Aggressive, malignant potential of GANT depends on the correlation of several features: tumor size > 5 cm, mitotic rate of 1–5 per 50 HPF, infiltration of adjacent structures, tumor necrosis and hemorrhage, infiltration of local structures (mucosa and serosa), and the presence of lymph node metastasis [14]. In our cases, except for tumor size, no other correlations were determined after the operation. Thus, we believe that the surgical excision that followed was optimal to satisfy all the oncologic principles.

Radical surgical resection seems to be the most appropriate, curative form of treatment for GANT. However, histopathologic analysis is essential not only to make the diagnosis (requiring electron microscopical confirmation of neurosecretory granules and neurotubules) and to plan for further treatment, but also to examine the biological characteristics of the tumors, particularly their response to newly synthesized drugs such as tyrosine kinase inhibitors.

For small and well defined tumors, cuneiform (wedge) resection is indicated.

For primary, localized, nonmetastatic GANT, complete surgical resection represents the only chance for cure [15]. Larger tumors, depending on localization, require extensive resection. Copious, life-threatening bleeding that requires urgent surgery is rare. In pediatric GANT cases, clinical outcomes have been favorable [16].

During the surgical excision of tumor, when we have found no enlarged lymph nodes, we have considered the diagnosis of GANT because lymph-node metastases are extremely rare and occur only in the advanced stages [17]. Lymphadenectomy is not necessary in most cases.

Metastatic disease has been noted in regional lymph nodes, liver, omentum, retroperitoneum, peritoneum and mesentery. In these cases, radical liver resection with adjuvant chemotherapy is the treatment of choice. Surgical treatment of malignant GANT is the primary therapeutic method, but because of the high malignant potential, tumor recurrence of the underlying disease is possible, and the five-year survival rate, despite adequate radical surgical procedures, ranges between 32% and 63% [10,11].

Conventional chemotherapy and radiotherapy is ineffective in the treatment of GANT. For metastatic CD117-positive tumors, tyrosine kinase inhibitors might be an appropriate palliative approach to treatment [18].

Imatinib mesilate, or Glivec (a tyrosine kinase inhibitor), was confirmed to be effective against metastatic or unresectable GANT. Imatinib (Glivec) is an inhibitor of tyrosine kinase that acts by specifically inhibiting a certain enzyme that is characteristic of a particular cancer cell, thus inhibiting and killing all rapidly dividing cells.

The primary therapy in both of our cases was a radical surgical excision. Histopathologic examination confirmed that the radical excision of tumor did not affect the regional lymph nodes or other portions of the digestive tract, and the tumor had a low degree of malignancy. In the second case, the tumor was on subserosal pedicle, which allowed radical surgery, and there was a lack of infiltration of the stomach and other organs, all of which contributed to a favorable outcome.

The recommended clinical follow-up for patients with high-risk tumors is CT or MRI examinations every 3 to 4 months during the first 3 years and then every 6 months for the next 5 years. In those with very low risk of malignancy, the control examinations should be performed every 6 months during the first 6 years. Modern diagnostic imaging procedures, like positron emission tomographic (PET) scans, are invaluable in the diagnosis of these tumors. However, PET scanning is not widely used in our contemporary practice because it is not readily available.

Data in the literature about the biological behavior of these tumors is scanty, but the largest number of relapses occur within the first 2 years after surgery, whereas in the low-risk group, tumor recurrence may not occur until decades later [14].

In conclusion, we believe that surgical resection of GANT is the only curative therapy to date, with the possibility of a high five-year survival rate of patients, even in cases of large tumors with distant metastases. The inability to make an adequate preoperative diagnosis causes a dilemma about the extent of the resection. Variables such as tumor size, mitotic index, tumor necrosis and hemorrhage, tumor infiltration, liver and lymph nodes metastases determine the malignant potential. In our patients, complete tumor excision was performed according to the principles of radical surgical resection. Further investigations are imperative for a detailed assessment of the biological behavior of GANT and for establishing treatment modalities.

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