CASE REPORT

Gastrointestinal autonomic nerve tumour of jejunum presenting as a perfore mass

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Abstract

Gastrointestinal autonomic nerve tumour (GANT) is a rare mesenchymal neoplasm of the gastrointestinal tract arising from the neural plexus of the intestinal wall. Herein, we present a 70-year-old male patient presenting with a clinical picture of acute abdomen. Examination of the specimen obtained from the small bowel by means of complete resection revealed a relatively soft submucosal mass measuring 4.5x3 cm in size with spindle morphology and high mitotic activity (>10 mitoses per 50 high-power fields). The tumour cells were strong positive for c-kit (CD117), S-100 protein and glial fibrillary acidic protein (GFAP), but did not harbour mutations in the c-kit and PDGFR genes. The diagnosis was based on light microscopy and immunohistochemical verification. We started tyrosine kinase inhibitor 400 mg/day. The patient is currently alive without metastasis at 28 months postoperatively. He is under close follow-up and survival data of the patient will be presented in the later studies.

Keywords: Gastrointestinal autonomic nerve tumour, S-100 protein, Stromal tumour, Small intestine, Jejunum.

Introduction

Gastrointestinal autonomic nerve tumour (GANT) was first described in 1984.[1] It is a rare variant of gastrointestinal stromal tumour (GIST) and occurs at an estimated frequency of 1% of all malignant gastrointestinal tumours.[2]

It is believed that GANTs are a subgroup of GISTs with autonomic nerve differantiation. But there is some evidence that these tumours are from different origins and may therefore exhibit distinct biological behaviours. Studies have shown that GISTs show a remarkable variability in their myoid, neural or autonomic neuronal mixed myoid/neuronal differentiation pathways. Ultrastructurally they reveal features suggestive of their myenteric plexus origin such as neuron-like cells with cytoplasmic processes, intermediate filaments, bulbous synapse-like, dense core neurosecretory granules.[1,3]

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GANTs remain mainly asymptomatic until the tumour reach a sufficient size to produce abdominal pain or mucosal ulceration with gastrointestinal bleeding. Symptoms could be related to the luminal obstruction, but this is a late event due to the serosal origin of the tumour. Herein, we present a case of GANT, which was located in the jejunum, had a high malignant potential and showed extensive neural differentiation and treatment with Imatinib in a 70-year-old male patient presenting to the emergency department (ED) with a clinical picture of acute abdomen.

Case Report

A 70-year-old male patient was admitted to the ED because of abdominal pain which was followed by nausea, vomiting and fever within the following 4 hours. The patient had diffuse abdominal pain that was more severe in the upper quadrant. The patient had no history of gastric ulcer or gastritis. His body temperature was 38°C, pulse rate was 112 beats per min, and his blood pressure was 100/60 mmHg. On physical examination, his abdomen was rigid and diffusely tender with rebound tenderness. Laboratory examinations showed leukocytosis (white blood cells [WBC] = 16.6K/uL); his blood haemoglobin level and platelet count were within normal limits. Electrolytes (urea-nitrogen, creatinine, transaminases, and alkaline phosphatase) were within normal limits. Abdominal ultrasonography showed moderate fluid collection in the abdominal cavity. Explorative laparotomy revealed a ruptured mass, 5x4x3 cm in size, in the proximal jejunum, and fluid in the abdominal cavity. Primary segmental resection of the jejunum with end-to-end anastomosis was performed. Following peritoneal lavage, abdominal drains were inserted, and then the abdomen was closed. The patient made a rapid post-operative recovery, and he was discharged on the fourth post-operative day.

Macroscopic examination of the fresh small bowel specimen measuring 27cm showed a nodular firm mass with areas of haemorrhage in the serosa. When the specimen was dissected, a relatively soft tumour measuring 4.5x3 cm in size, arising from the submucosal layer 3cm far from the closest surgical margin, and showing deep ulceration and necrosis was exposed (Figure-1).

On microscopic examination, a neoplasm extending from the submucosa to the serosa was observed. There was coagulation necrosis in several foci.The neoplasm was composed of spindle cells without a definite organoid pattern. The number of mitoses was counted in cellular areas, and mitotic activity was found to be >10 per 50 high-power fields (Figure-2 A-C). In order to establish a histopathological diagnosis and to differentiate the neoplasm which had morphology suggestive of GANT, immunohistochemical staining was performed. Strong immunoexpression of CD117 [(c-kit, 1:100, Thermo, UK) (Figure-2D)] and synaptophysin (clone SP11, 1:100, Thermo, UK) was observed. Strong positivity for glial fibrillary acidic protein [(clone GA-5, 1:100, Therma, UK) (Figure-3A)] and S-100 (Leica, UK) protein was a striking finding (Figure-3B). On the other hand, the tumour cells were negative for desmin (clone d33, Thermo,UK), CD34 (clone QBEnd/10,1:50,Thermo,UK) and smooth-muscle-actin (clone 1A4, Scytek, The Netherlands). Immunohistochemical (IHC) staining for Ki67 (MIB-1, clone GM010, 1:100, Genemed, Germany), a marker of proliferation, was positive in 7% of the tumour cells. No atypical cells were observed in peritoneal lavage fluid.

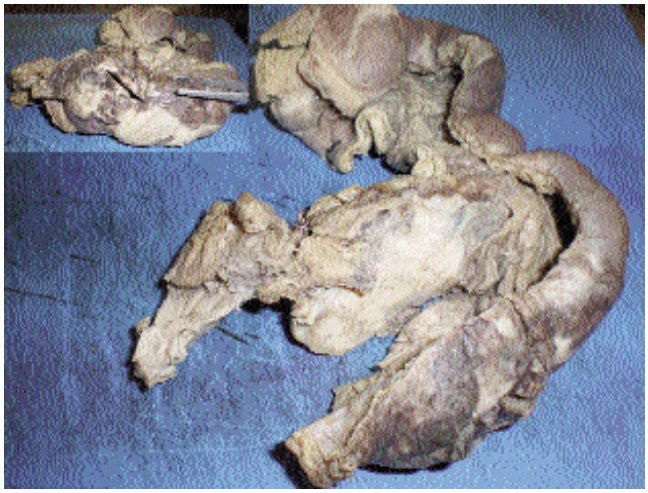

Figure-1: Nodular mass with areas of haemorrhage in the serosa. (insert). In dissected resection an ileal mass arising from the submucosal layer, with grey-white color.

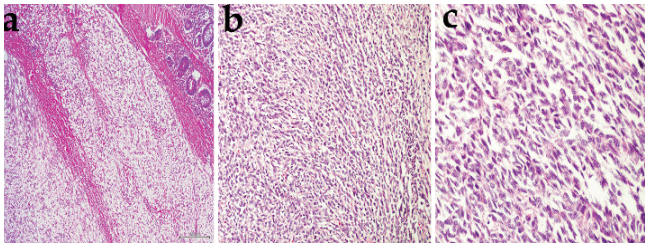

Figure-2: Histopathologic findings (a) neoplastic cells showed solid infiltration beneath the mucosa (H.Ex10). (b) In this tumour, the neoplastic cells are spindle shaped and are arranged without a definite organoid pattern (H.Ex20), (c) with high mitotic activity (H.Ex40).

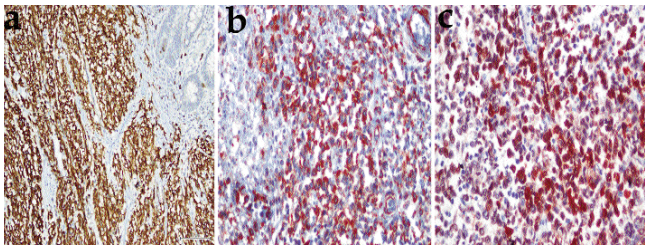

Figure-3: Immunohistochemical findings; (a) Strong positivity for CD 117 (c-k?t) in tumour cells. C-kit positivity is mainly localized at the cell membrane (x20). (b) Strong immunreactivity for GFAP (x40). (c) Extensive S-100 positivity in tumour cells (x40).

Dioxyribonucleic acid (DNA) was extracted from paraffin embedded tissue and analysed for mutation in exons 9, 11, 13 and 17 of the c-kit gene, and exons 12, 14 and 18 of the PDGFR gene using denaturing high-performance liquid chromatography as per methodology described by Cohen et al.[4] The tumour was CD117 positivie, but did not harbour mutations in the c-kit and PDGFR genes.

Based on the pathologic and immunohistochemical findings, our case was reported as GANT. The mass was completely resected. Both surgical margins were negative for tumour cells. The patient did not develop post-operative complications, and screening tests did not show metastasis. Thus, he was discharged on the fourth post-operative day.

Discussion

The rate of differentiation in GISTs is variable, and neural differentiation is markedly higher, especially in tumours located in the duodenum and jejunum. Interestingly, contractile force of the stromal cells is most expressed in the oesophagus and rectum, the tumours of which show the most obvious evidence of smooth muscle differentiation. On the other hand, neuronal tumours of GANT type are more common along the small bowel facilitating the coordination of activities.[5] These tumours represent a distinct sub-category of gastrointestinal tumours.

GANT was first described in 1984.[1] GANT is a specific type of stromal tumour arising from the neural plexus of the intestinal wall and supported by its ultrastructural features. Histologically, GANTs present a spindle and occasionally epithelioid cells population. Ultrastructural and IHC studies are needed to establish the diagnosis. The presence of dense-core neurosecretory-type granules and skeinoid collagen fibers on electron microscopy are

associated with neural differentiation.[1,3]

IHC studies have demonstrated that the tumour is often reactive to markers of nerve tissues such as neuron-specific enolase (NSE), synaptophysin, S-100 protein, neurofilament and chromogranin. These proteins are normally expressed by neurons from the autonomic enteric nerve plexus, supporting a histogenesis of GANTs from enteric autonomic plexuses of Mesiner or Auerbach.[6]

In studies of GANT, 100% positivity for c-kit was noted, vimentin 92%, neuron specific enolase 90%, CD34 58%, S-100 39% to 44%, synaptophysin 31%, chromogranin A 11%, neurofilament 16%, α smooth muscle actin 10%, vasoactive intestinal peptide 20%.[6,7] In the present case, the tumour cells were strongly positive for S-100 protein, a marker of neural differentiation. An IHC study of a series of 10 cases with GANT found S-100 protein positivity in 60% (6/10) of the cases.[3] The authors suggested that electron microscopy was essential to differentiate GANT from other GISTs and that IHC examination was of limited value without ultrastructural evaluation. The rarity of GANT may therefore be a consequence of the unavailability of routine electron microscopic analysis.

At the histochemical level, GANTs without smooth muscle differentiation preserve features consistent with a central or peripheral schwannian/glial line, such as S-100 protein and glial fibrillary acidic protein (GFAP) and show ultrastructural features consistent with neuronal differentiation rather than schwannian differentiation.[8] Although we were not able to perform electron microscopic examination in our case, strong GFAP and S-100 positivity may support this idea.

In the majority of GANTs, the primary site of the tumour is the stomach, duodenum, jejunum and ileum, but the oesophagus, rectum, bladder or colon have also been reported in some cases. Localization of these tumours in the small bowel were as follows: 20% in the duodenum, 45% in the jejunum, and 35% in the ileum.[6] This case is compatible with the literature as it was located in the jejunum.

These tumours usually manifest with abdominal pain, palpable mass, gastrointestinal bleeding and the patients may present with bowel obstruction and associated symptoms.[6] GANTs can present as an asymptomatic mass (found at the time of surgery or imaging studies for other reason) or can cause non-specific symptoms such as anorexia, weight loss, gastrointestinal obstruction or metastases.[9] GANTs can present also as a large intra-abdominal abscess.[10] Our case which had the clinical picture of acute abdomen indicated the involvement of serosa.

For jejunal and ileal tumours, a diametre >5 cm, >5 mitoses per 50 high-power fields and the presence of coagulation necrosis are poor prognostic factors. Using the Miettinen classification, our case was evaluated to have a high malignant potential due to a tumour diametre of 4.5cm, its submucosal localisation, cellularity, low nuclear atypia, the presence of coagulation necrosis, and a mitotic rate of >10 mitoses per 50 high-power fields. These tumours pose a high risk for intra-abdominal dissemination and liver metastasis.[11] Over 10% rate of Ki-67 positive nuclei was found to be significantly associated with metastasis and tumour-related mortality. In the present case, screening tests after the diagnosis of GANT did not show metastasis, but, it is too early to make a definite statement at the 28th post-operative month, and we think that close follow-up is necessary due to 7% Ki-67 positivity.

To date there is no difference in the surgical treatment of GANTs and GISTs. But there is some evidence that these tumours are from different origins and may therefore exhibit distinct biological behaviours. However, due to the limited number of reported GANTs, further investigations would be necessary to fully characterise these tumours with respect to future treatment decisions.

In literature, radical surgical resection appears to be the most promising and solely curative treatment regimen for gastrointestinal autonomic nerve tumours.[6] In our case, complete resection without any extended lymphadenectomy was performed, and proximal and distal surgical margins were negative for tumour cells. However, the small bowel serosa was positive for tumour cells, posing a potential for tumour seeding into the peritoneal cavitiy.

GISTs main risk factor is the histological grade which depends on mitotic count and tumour size. High mitotic count (>5 mitoses per 50 high power fields) and tumour size (>5cm) is associated with a high risk of recurrence or metastatic disease. Despite their low grade of malignant histological apperance, GANTs are associated with poor prognosis due to high recurrence and metastases rate.[6] Although it does not have sufficient number of patients in clinical follow-up, but GANTs are fatal and must be considered malignant. We are aware of the fact that present tumour diameter <5 cm, >5 mitoses per 50 high-power fields, and the presence of serosal involvement means that the patient requires a close follow up.

Imanitib (thyrosine kinase inhibitor) is used as neoadjuvant and/or adjuvant therapy in locally advanced

or metastasised GIST. But to date there are no reports on their use in CD117 positive GANT. We considered our case as having high malignant potential, and started tyrosine kinase inhibitor 400 mg/day; radiotherapy was not administered.

Conclusion

Large-scale, long-term follow-up studies in patients with GANTs of the small bowel with high malignant potential will provide more insight into the biological behaviours and treatment of these tumours.

Acknowledgement

We are grateful to Associate Professor Berna Savas, for her assistance with molecular analysis as well as for a critical review of the manuscript.

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