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Autore/i: Giorlandino A, Caltabiano R, Gurrera A, Lanzafame S

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CASE REPORT

Gastrointestinal stromal tumour of the stomach with osseous differentiation: a case report

A. GIORLANDINO[1], R. CALTABIANO[1], A. GURRERA[2], S. LANZAFAME[1]
[1] Department G.F. Ingrassia, Section of Anatomic Pathology, University of Catania, Italy; [2] Division of Pathology, Vittorio Emanuele - Policlinico Hospital, Catania, Italy

Key words

GIST • Osseous differentiation • C-KIT

Summary

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal tract, while osseous metaplasia of this tumour is an unexpected event. To date, no cases have been reported in the literature. Herein, we report a case of a 60-year-old man affected by a GIST with benign osseous metaplasia and mature bone formation. We also discuss the pathogenesis of intratumoural ossification and review the relevant literature. The prognostic significance of ossification in GIST remains unclear because of the limited cases reported.

Introduction

Gastrointestinal stromal tumours (GISTs), accounting for 0.1%-3.0% of all gastrointestinal malignancies, are the most common mesenchymal neoplasm of the gastrointestinal tract and should be differentiated from other mesenchymal tumours. GISTs occur primarily in older patients of either sex, with annual incidences between 11 and 19.6 per 10^6 population worldwide [1]. GISTs show a wide spectrum of histological appearances and clinical features. Histologically similar tumours span a clinical spectrum from benign to aggressively malignant, and this has lead to a number of attempts to better identify pathological features (both morphological and molecular) that may predict subsequent behaviour, or suggest a specific clinical syndrome [2]. More than half of all GISTs occur in the stomach and about one-third in the small intestine. Most GISTs arise sporadically, but may also occur in association with a number of clinical syndromes, including Carney triad and Carney-Statakis syndrome [3]. Some cases are reported during pregnancy [4]. The most common clinical presentations include gastrointestinal bleeding, vague abdominal complaints and incidental findings. Small intestinal tumours may cause obstruction with or without intussusceptions. Typically, malignant GISTs disseminate by coelomic spread within the abdomen and/or metastasise to the liver and other organs such as the ovary. Extra-abdominal metastases are extremely unusual [3]. GISTs may also occur in association with other malignancies and may be discovered incidentally during management of other tumours [5 6]. GIST may range from an innocuous mural or subserosal nodule to a large complex mass that may be transmural in the gastric or intestinal wall, or present as multiple peritoneal nodules.

Histologically, about 25% of gastric GISTs have spindle or epithelioid morphology, and a number of cases have mixed features. Most typical spindle cell GISTs are moderately or highly cellular and are relatively monomorphic, with the cells arranged in sheets, ill-defined fascicles or perhaps palisades reminiscent of schwannoma. Mitoses vary from very occasional to abundant. Nuclear pleomorphism is more common in epithelioid tumours, with abundant myxoid stroma. Chondroid metaplasia or calcifications may also occur, and some tumours show rhabdoid morphology [1 7].

Most sporadic GISTs are caused by the constitutive activation of KIT, a type III receptor tyrosine kinase, which is encoded by the KIT (c-kit) gene located on chromosome 4q12. The mechanism of activation in most sporadic GISTs is an alteration of the structure

Correspondence
Alexandra Giorlandino, Department G.F. Ingrassia, Section of Anatomic Pathology, University of Catania - Santa Sofia 87 street, 95123 Catania, Italy - Tel. +39 095 3782022 - Fax +39 095 3782023 - E-mail: alexandragiorlandino@hotmail.it

of the receptor's extracellular or cytoplasmic domains caused by somatic mutations of the c-kit gene, which leads to dimerisation and autophosphorylation of KIT with subsequent activation of signal transduction cascades in the absence of ligand binding [8]. Inhibition of KIT activity by a specific tyrosine kinase inhibitor, imatinib, often results in dramatic clinical responses [9]. In contrast to GISTs associated with somatic mutations, GISTs caused by germline mutations are extremely rare. Most GISTs lacking KIT mutations harbour mutations in platelet-derived growth factor receptor alpha polypeptide (PDGFRA), a tyrosine kinase receptor that is highly homologous with KIT. PDGFRA mutations are more common in tumours with gastric localisation, which often display a myxoid and epithelioid phenotype. KIT and PDGFRA mutations appear to be mutually exclusive. We report a rare case of GIST with histological osseous metaplasia and mature bone formation.

Case report

A 60-year-old man presenting with abdominal pain was referred to our hospital. His medical and family history was unremarkable. He had no history of previous abdominal surgery. On physical examination, he showed mild tenderness in the upper abdomen quadrant area. Oesophagogastroduodenoscopy showed in the gastric fundus, below the cardias along the greater curvature, a large ulcer crater with raised edges and bottom covered by fibrin with signs of recent bleeding. Following biopsy, histological examination detected the presence of a GIST. Twenty days later, the patient underwent surgery. No evidence of local invasion or distant metastasis was found during surgery. At gross examination, the tumour was 7.6 cm in maximum diameter, projected into the gastric lumen as an endophytic polypoid submucosal growth and prone to surface ulceration and bleeding. It was a well-circumscribed, nodular mass that lacked a true capsule. The cut surface was grey to pink with an increased consistency. Histological examination revealed a proliferation of spindle cells with a mitotic count < 5 mitoses/50 HPF with areas showing focal osseous differentiation [Fig. 2A]. Interlacing bundles of uniform spindle-shaped cells with ovoid and elongated nuclei and fibrillary eosinophilic cytoplasm were observed. The stroma was hyalinised and with focal calcification with areas of metaplastic ossification. Osteoblasts and osteoclasts surrounded the surface of the heterotopic bone. Haversian canals were occasionally identified in the bony trabeculae.
Immunohistochemical studies revealed positive staining for CD34 [Fig. 2B] and CD117 (c-KIT) [Fig. 2C]. Based on the above findings, the tumour was diagnosed as a GIST with osseous differentiation and low-grade malignancy. The follow-up period was 12 months, and there was no recurrence.

Fig. 1. Histological examination revealed proliferation of spindle cells with a mitotic count < 5 mitoses/50 HPF with areas showing focal osseous differentiation.

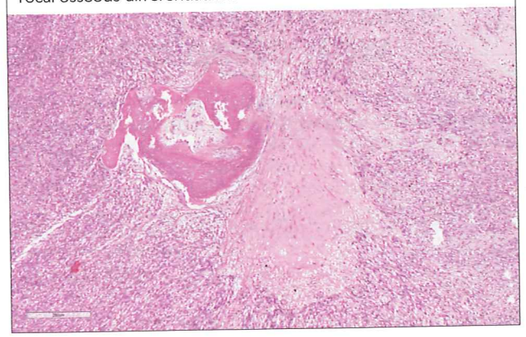
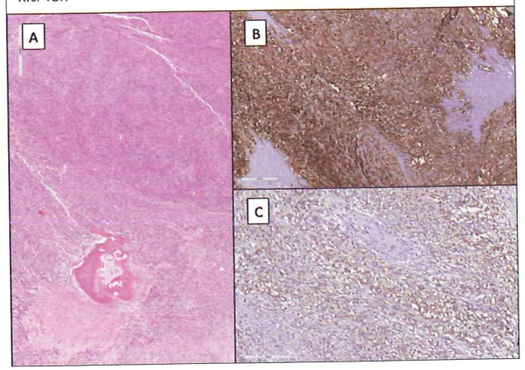


Fig. 2. The stroma was hyalinised and extensive calcification with areas of metaplastic ossification was present (A). Cells showed strong staining for CD34 (B) and moderate staining for CD117 (c-kit) (C).



Discussion

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract, arising from the interstitial cells of Cajal, primarily in the stomach and small intestine.
They manifest a wide range of morphologies, from spindle cell to epithelioid, but are immunopositive for KIT (CD117) and/or DOG1 in virtually all cases [1].
GISTs may be divided into three main histologic categories: spindle cell type, epithelioid type and mixed type. Spindle cell GISTs are composed of short fascicles and whorls, characterised by spindle-shaped cells with ovoid or elongated nuclei and paranuclear vacuolisation; the stroma may be variable and show areas of myxoid change, calcification or metaplasia. Epithelioid GISTs are arranged in nests or sheets, characterised by rounded cells with abundant clear cytoplasm and vesicular nuclei. A lower percentage of GISTs shows both histological patterns in different areas of the tumour. The degree of cellularity and nuclear pleomorphism of GISTs vary considerably and do not correlate directly with a worse prognosis. The three main parameters that correlate with prognosis are the tumour location, size and mitotic rate [10].
Although most tumours are localised at presentation, up to half will recur in the abdomen or spread to the liver. The growth of most GISTs is driven by oncogenic mutations in either of two receptor tyrosine kinases: KIT (75% of cases) or PDGFRA (10%). Treatment with tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib, or regorafenib is effective in controlling unresectable disease; however, drug resistance caused by secondary KIT or PDGFRA mutations eventually develops in 90% of cases. Adjuvant therapy with imatinib is commonly used to reduce the likelihood of disease recurrence after primary surgery, and for this reason assessing the prognosis of newly resected tumours is one of the most important roles for pathologists.
Approximately 15% of GISTs are negative for mutations in KIT and PDGFRA. Recent studies of these so-called wild-type GISTs have uncovered a number of other oncogenic drivers, including mutations in neurofibromatosis type I, RAS genes, BRAF and subunits of the succinate dehydrogenase complex. Routine genotyping is strongly recommended for optimal management of GISTs, as the type and dose of TKI used for treatment is dependent on the mutation identified.
Focal calcification within a large GIST especially within necrotic areas has been reported [11 12]. Most calcifications in GISTs are usually of a circumscribed patchy type [13 14]. Rare cases with extensive calcification that constitutes the major portion of the tumour are reported [11]. Calcification has been suggested to indicate less aggressive tumour behaviour, and a slowly progressing tumour shows dystrophic calcification within the area of tumour hyalinisation. Calcification within GIST has been previously reported [15 16], but osseous differentiation is an unexpected event. Heterotopic ossification is not usually seen in neoplasms and is more often seen in reparative and degenerative conditions.
In our case, osseous differentiation was defined by the presence of heterotopic normal bony tissue within the GIST probably related to ischaemia, necrosis, or inflammation in the tumour or surrounding tissue. The pathogenesis of osseous differentiation is still unclear and various theories have been proposed. Currently, multiple cell mediators, including platelet-derived growth factor whose receptor is frequently mutated in gastric GIST, are thought to play a role in the regulation of ectopic bone formation. Bone morphogenic proteins (BMP) play an important role in bone formation by inducing local ossification and synthesising ground substance and collagen, but the final step in bone formation depends on adequate concentrations of calcium and phosphate. As reported by morphoproteomic analysis to define the histogenesis of the heterotopic ossification in tumours [17], this phenomenon could be the result of pluripotent stromal cells that undergo differentiation to form osteoblasts rather than tumour cells undergoing osseous metaplasia.
In conclusion, we present a very rare case of GIST with extensive osseous differentiation. The prognostic significance of ossification in GIST remains unclear because no cases have been reported in the literature. A careful search for cellular areas and the judicious application of immunostaining will thus make it possible to make a correct diagnosis. Therefore, when osseous nodules are encountered in the gastrointestinal tract, the possibility of a GIST should be considered.

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