Pathology – Research and Practice 211 (2015) 892–895

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Teaching cases

Gut wall replacing type of gastrointestinal stromal tumor presenting as a perforation of the ileal diverticulum

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ARTICLE INFO

Article history:
Received 23 March 2015
Received in revised form 5 May 2015
Accepted 8 May 2015

Keywords:
Gastrointestinal stromal tumor
Deverticulum
Meckel's deverticulum
Perforation

ABSTRACT

Gastrointestinal stromal tumors (GISTs) usually form a well-circumscribed mass. Very rarely, however, sporadic GISTs show gut-wall replacing growth, similar to the diffuse hyperplasia of interstitial cells of Cajal (ICC) observed in patients with neurofibromatosis type 1 (NF1) and hereditary GIST. Here we describe a patient with ileal perforation caused by this unusual type of GIST. An 82-year-old man was admitted to the emergency department with sudden abdominal pain. Following a provisional diagnosis of perforation of Meckel's diverticulum, he underwent segmental resection of the small intestine. Macroscopic examination revealed a diverticulum-like structure 2.5 cm in size near the site of mesenteric attachment of the ileum. Histological examination showed diffuse and nodular proliferation of spindle cells positive for c-KIT and CD34 that had replaced the muscularis propria of the small intestine. Mutational analyses of the lesions revealed monoclonality of proliferating cells with a somatic mutation in c-*kit* exon 11 (p.Leu576Pro). Gut-wall replacing type of GIST should be recognized as a specific type of GIST causing diverticulum-like structures of the gastrointestinal tract.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms in the human gastrointestinal (GI) tract. These tumors are thought to be derived from interstitial cells of Cajal (ICC) or their stem cell-like precursors [15]. GISTs are KIT-signaling-driven neoplasms caused by gain-of-function mutations of *c-KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) oncogenes through a ligand-independent activation of type III receptor tyrosine kinases [2,10]. Mutations of c-*KIT* exon 11 (juxtamembrane domain) are the most common type found in GISTs.

Most GISTs are sporadic and usually present as round, well-circumscribed mass lesions in the wall of the GI tract, with or without hemorrhage or necrosis. Diffuse growth of ICCs in the GI tract, called ICC hyperplasia, has been observed in patients with specific tumor syndromes, including neurofibromatosis type 1 (NF1), the Carney triad, and familial GIST syndromes caused by germline mutations of the *c-KIT* and *PDGFRA* genes [12,15,21]. Proliferating spindle cells form a diffuse band or minute nodules in the region of the mesenteric plexus of Auerbach, and these proliferative lesions are almost exclusively microscopic, measuring less than 10 mm [4,11]. In contrast, ICC hyperplasia is rare in patients with sporadic GIST, with most being nodular proliferations of ICC-like cells. This report describes a patient, initially presenting with perforation of the diverticulum, who was found to have a sporadic GIST with a diffuse longitudinal growth pattern. This specific type of GIST should be included in the differential diagnosis of patients with diverticulum-like structures of the GI tract, including duplication.

1.1. Case presentation

An 82-year-old man was admitted to the emergency department with sudden abdominal pain. Abdominal computed tomography (CT) showed a small amount of free air around the liver. He was preliminarily diagnosed with a perforation of Meckel's diverticulum and underwent emergency surgery. Laparotomy revealed a perforated diverticulum-like lesion 80 cm proximal to the ileocecal valve, and segmental resection of the small bowel was performed. The lesion was located midway between the mesenterium attachment and its opposite side (Fig. 1). There were no recurrences or metastases at follow-up 22 months after surgery. He has no features of NF-1 or other relevant familial history.

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http://dx.doi.org/10.1016/j.prp.2015.05.001
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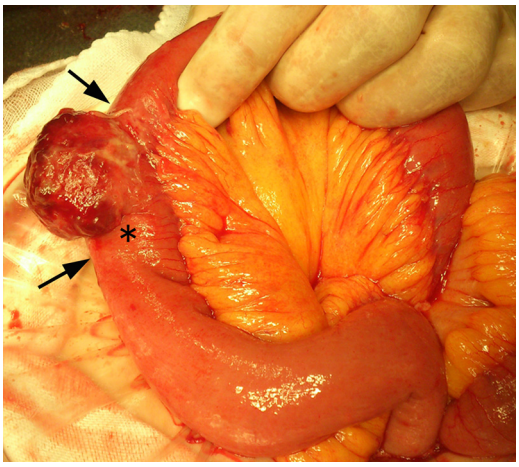

Fig. 1. Laparotomy findings at surgery. A diverticulum-like lesion was observed 80 cm proximal to the ileocecal valve; note the hemorrhagic serosa covering the lesion. The site of the diverticulum (asterisk) was not contralateral to the mesentery. The arrows indicate the side opposite the mesenterium attachment.

2. Material and methods

The surgical specimen was fixed in 10% formalin, and processed for routine histological analyses. Immunohistochemical analysis was performed with the Ventana Benchmark system.

For mutational analysis, DNA was extracted from formalin-fixed paraffin embedded tissue. Nodular and diffuse lesions and surrounding normal tissue were macrodissected from 10 sections 10 μm in thickness. Exons 9, 11, 13 and 17 of the *c-KIT* gene and exons 12 and 18 of the *PDGFRA* gene were amplified by polymerase chain reaction (PCR) and the products sequenced in both directions. The sequences of primers for *c-KIT* exons 9, 13, 17 and *PDGFRA* exons 12 and 18 have been described [8,21]. c-KIT exon 11 was amplified using the primers 5′-TGTTGAGGAGATAAATGGAA-3′ (forward) and 5′-GACCAAAACTCAGCCTGTTT-3′ (reverse).

3. Results

Macroscopic examination of the specimen revealed a diverticulum-like lesion 2.5 cm in size with a pinhole perforation at its base (Fig. 2). Histologically, the diverticular structure was lined by intact mucosa, but there was no evidence of ectopic gastric mucosa or pancreatic tissue. The diverticular wall consisted of two components: nodular and diffuse lesions of proliferating spindle cells. Diffusely proliferating spindle cells had completely replaced the muscularis propria of the gut wall. Both the nodular and diffuse lesions consisted of spindle cells arranged in short intersecting fascicles (Fig. 3). The tumor cells had elongated to plump nuclei and eosinophilic cytoplasm. Significant atypia was not observed and the mitosis rate was 1/50 high power field. Spindle cells of both lesions were immunohistochemically positive for c-KIT, CD34 and DOG1 and negative for desmin and S-100. There was no evidence of ICC hyperplasia or microscopic GISTs in the remaining bowel segment.

Mutation analyses revealed a point mutation at codon 576 (p.Leu576Pro) in c-*KIT* exon 11 in both nodular and diffuse lesions. Otherwise, there were no mutations in c-*KIT* exons 9, 13, and 17 and *PDGFRA* exons 12 and 18. Analysis of the surrounding normal tissue demonstrated wild-type sequence for *c-KIT* exons 9, 11, 13 and 17 and *PDGFRA* exons 12 and 18.

4. Discussion

GISTs in this patient had a diverticular appearance and growth pattern replacing the gut wall, lesions superficially mimicking diffuse ICC hyperplasia in patients with germline mutations in the *NF-1*, *c-KIT* and *PDGFRA* genes. ICC hyperplasia has been observed in microscopic lesions in patients with NF1 and hereditary GIST. These lesions usually consist of proliferating c-KIT positive cells, primarily in Auerbach's plexus, preserving the structures of the inner and outer circular muscle layers [22]. In our patient, however, tumor growth had replaced the full thickness of the gut wall. Moreover, the diffuse and nodular lesions in this patient had the same somatic mutations, indicating monoclonal growth of ICC-like cells, and contrasting with the polyclonal nature of ICC hyperplasia [6]. To date, six patients with GIST replacing the full thickness of the muscularis propria have been described in the English medical literature (Table 1) [1,9,18,22,23]. All of these tumors were sporadic and all mutations were observed in exon 11 of the *KIT* gene, although the lesion in one patient was microscopic. These lesions have been called, for example, sporadic segmental ICC hyperplasia (microscopic GIST) and long segmental hyperplasia of ICC, which do not necessarily imply that these lesions are neoplastic. The neoplastic nature of these tumors, however, indicates that the gut-replacing

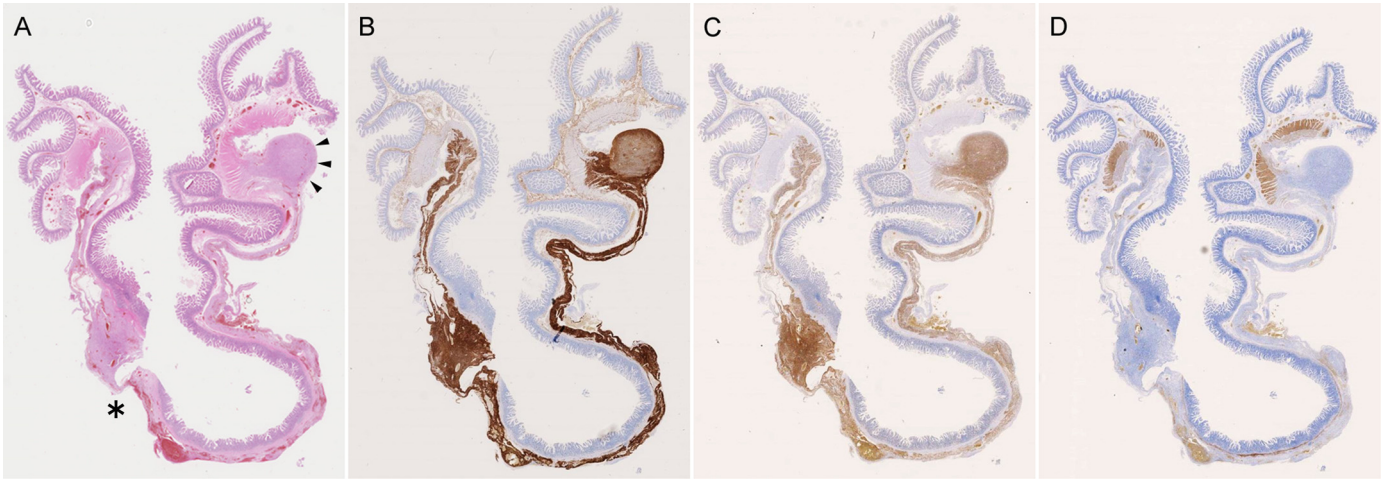

Fig. 2. Loupe views of the diverticulum-like lesion. (A) The diverticulum-like lesion showed diffuse and nodular proliferation of spindle cells (arrowheads); the asterisk indicates the point of perforation. The entire lumen of the diverticulum-like structure was covered with epithelium continuous with the non-neoplastic mucosa. (B–D) Immunohistochemical expression of (B) CD34, (C) c-KIT, and (D) desmin. Desmin immunostaining showed that the existing muscle layer and part of the muscularis mucosae had been replaced by tumor cells.