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Sporadic diffuse segmental interstitial cell of Cajal hyperplasia harbouring two gastric gastrointestinal stromal tumours (GIST) mimicking hereditary GIST syndromes

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ABSTRACT

INTRODUCTION: Gastrointestinal stromal tumours (GISTs) are thought to derive from or differentiate towards the interstitial cells of Cajal (ICC) as most demonstrate a similar immunoprofile: CD117+, CD34+ and DOG1+. ICC hyperplasia refers to KIT-expressing microscopic spindle cell proliferations involving the myenteric plexus.
CASE REPORT: 74 year-old male presented with a 5-year history of heartburn and dysphagia. Imaging revealed a 4 cm GIST in the gastric fundus. Pathology of the resected specimen revealed diffuse segmental ICC hyperplasia harbouring two macroscopic GISTs and a 'tumorlet'. A mutation in c-KIT exon 11 was detected in both the solid and the diffuse components.
DISCUSSION: ICC hyperplasia can occur either as a sporadic focal lesion or in a syndromic setting, known to predispose to multiple GIST tumours at different sites. The majority of cases of sporadic ICC hyperplasia previously reported were of localised type. The hereditary form is mostly caused by germline mutations in *c-KIT* and *PDGFRA* or in patients with NF-1 andpresents as a diffuse hyperplasia, usually with a confluent, nodular or multifocal growth pattern.
CONCLUSION: We describe a diffuse form of sporadic ICC hyperplasia harbouring multifocal GISTs, mimicking diffuse ICC hyperplasia in hereditary GIST syndromes. Detection of somatic *c-KIT* exon 11 mutation ruled out a hereditary disorder.

1. Introduction

Gastrointestinal stromal tumours (GISTs) are the most common primary mesenchymal neoplasms of the tubular gastrointestinal (GI) tract. They can occur at any site but are most frequent in the stomach (60%) and small bowel (35%). These tumours are KIT (CD117)-positive and KIT-signalling-driven neoplasms caused by gain-of-function somatic mutations in the c-*KIT* (c. 80%) or platelet-derived growth factor receptor alpha (*PDGFRA*, c. 10%) genes with varied histological features, including spindle cell, epithelioid and rarely pleomorphic morphology [1]. Molecular biology has contributed to the understanding of these lesions, but ± 15% of cases have no *KIT* or *PDGFRA* mutations [2]. Recently, mutation in BRAF (V600E) has been found in c. 13% of wild-type *KIT/PDGFRA* cases [3].

GISTs are currently thought to derive from or differentiate towards the gastrointestinal 'pacemaker cells', the Interstitial Cells of Cajal (ICCs), which instigate peristalsis in the stomach and intestine [4]. These cells are CD117+, CD34+ and DOG1+ slender bipolar mesenchymal cells forming a network surrounding the autonomic nerves of the Auerbach plexus and are also distributed within the internal and external layers of the muscularis propria [4,5]. Most GISTs demonstrate an immunoprofile similar to that of ICCs: CD117+, CD34+ and DOG1+ [4].

ICC hyperplasia refers to KIT-expressing, microscopic, focal or diffuse spindle cell proliferations involving the myenteric plexus, which may occur either as a sporadic lesion or present in a syndromic setting known to predispose to multiple GIST tumours at different sites: hereditary GIST syndromes caused by germline mutations in *c-KIT* [6] and *PDGFRA* [7], patients with neurofibromatosis type 1 (NF-1) [8], Carney's triad with mutations

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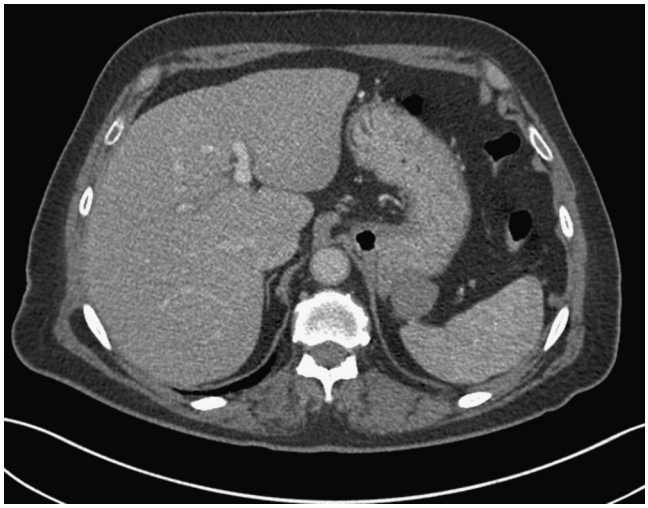

Fig. 1. Contrast-enhanced computerized tomography showing an exophytic 4 × 3 × 3 cm low-density nodule arising from the posterior wall of the gastric fundus.

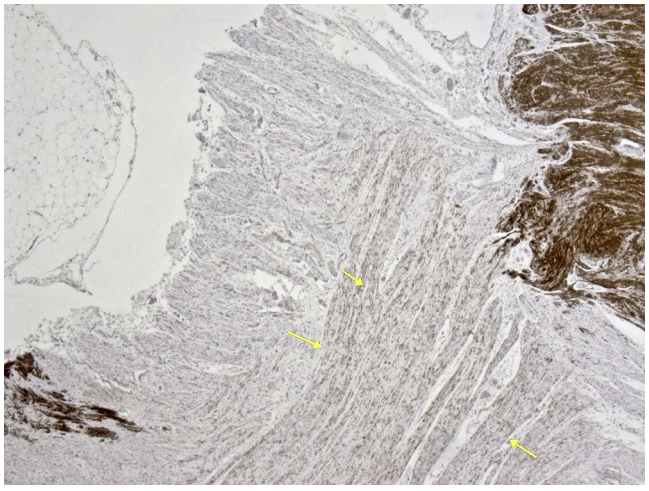

Fig. 2. Hyperplasia of muscularis propria (arrows) between main tumour (right) and subserosal nodule (left) highlighted by immunohistochemistry for DOG1.

in succinate dehydrogenase subunits [9] and in a case of congenital intestinal neuronal dysplasia [10]. These syndromic forms of ICC hyperplasia may either involve the plexus diffusely or form discrete micronodules that coalesce to form grossly recognisable small tumours.

We present a case of sporadic diffuse segmental ICC hyperplasia harbouring two macroscopic GIST lesions and one 'tumorlet' thus mimicking a syndromic condition, to our knowledge previously unreported. Written consent from the patient was obtained for publication.

2. Case report

A 74 year-old man with a longstanding history of chronic gastritis and effective eradication of *Helicobacter pylori*, presented with aggravated heartburn and dysphagia at the level of the xiphisternum for five years. After several upper GI endoscopies showing mild atrophic gastritis in the antrum, had a computerised tomography that revealed a 4 × 3 × 3 cm low-density nodule containing a small focus of calcification arising from the posterior wall of the gastric fundus, suspicious of an exophytic GIST (Fig. 1). The case was discussed in a sarcoma multidisciplinary meeting with a consensual decision to proceed to surgery due to tumour size and symptoms. The patient underwent laparoscopic excision of the GIST and was discharged after five days of operation. He remained disease free after five months of follow up and did not receive adjuvant treatment. There was no history of NF-1 or other relevant family history.

2.1. Pathological findings

The resection specimen was composed of a gastric wall measuring 5.5 × 4 × 3.5 cm. There were two papillary tumour masses lightly adherent to the serosal surface, the larger measuring 4 × 3 × 3 cm and the smallest 3 × 3 × 2.5 cm, both part of a single mass that fragmented during contraction on removal and fixation. There was one separate firm, white nodule measuring 0.8 × 0.7 × 0.4 cm on the serosa and involving the muscularis propria, 3.5 cm from the margin (Fig. 2).

Both the large and the smaller visible nodules had identical morphology, with compact arrangements of relatively uniform spindle cells with elongated nuclei, inconspicuous nucleoli and small, well-defined paranuclear cytoplasmic vacuoles. There was no necrosis. The tumours were covered by an intact peritoneal surface. The mitotic index was 4 per 50HPF. In addition, the Ki67 index, discounting infiltrating lymphoid cells, was 2.5% in the larger tumour and 6% in the smaller nodule.

There was very subtle diffuse infiltrative component within the muscularis propria, highlighted on the immunohistochemistry for DOG1 and CD117 (Fig. 3). The tissue immediately adjacent to the staple line contained a further microscopic focus of GIST ('tumorlet') measuring 0.7 × 0.3 mm (Fig. 4).

Additional staining with CD117 and DOG1 demonstrated a markedly increased density of immunoreactive cells in the apparent uninvolved muscularis propria in the vicinity of the peduncle of the large tumour.

2.2. Molecular findings

Using capillary electrophoresis single-strand conformation analysis (CE-SSCA), a deletion involving codon 560 in *c-KIT* exon 11 (c.1679_1681del p.-Val560del) was detected in both the solid and the diffuse components. This result was confirmed on a second, independent investigation. There was no detectable mutation in the PDGFRA gene.

3. Discussion

ICC hyperplasia can present as a sporadic lesion or as a syndromic setting known to predispose to multiple GISTs at various sites in the GI tract. The majority of cases of sporadic/incidental ICC hyperplasia previously reported were of localised type [11,12]. Diffuse type ICC hyperplasia is usually hereditary, rarely causes thickening of the muscularis propria and generally exhibits a confluent, nodular or multifocal growth pattern. These hereditary lesions may grow further to form discrete GIST nodules, similar to microscopic GISTs in their circumscription and their gradual merging with the surrounding muscle layer [13].

Diffuse ICC hyperplasia has been found in a variety of GI motility disorders. A few cases have been reported of GISTs arising in a diverticulum, but there was no description of diffuse ICC hyperplasia [14,15]. Agaimy et al. described two cases of sporadic ICC hyperplasia showing diffuse longitudinal microscopic growth completely replacing the muscularis propria and mimicking diffuse ICC hyperplasia in hereditary GIST syndromes [16]. One of the cases was associated with a small bowel diverticulum and the other was a finding in a sigmoid specimen resected for a villous adenoma. This diffuse growth in a sporadic form had not been previously reported.

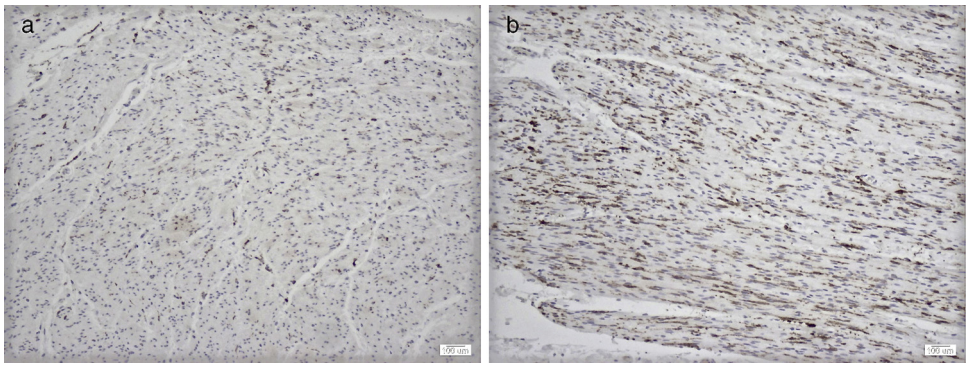

Fig. 3. (a) Uninvolved area of muscularis propria; (b) subtle infiltrative component in the muscularis propria contrasted by immunohistochemistry for DOG1.

In our case, the gastric specimen exhibited a diffuse hyperplasia of ICC in a thin and apparent uninvolved muscularis propria, harbouring two well-circumscribed GISTs and a GIST 'tumorlet', consistent with multifocal ICC hyperplasia. Although this pattern mimics the diffuse hereditary form in patients with germline mutations in NF-1, *c-KIT* or *PDGFRA*, the findings in our case are different in terms of extent (diffuse yet segmental). Furthermore, the detection of a somatic *c-KIT* mutation in exon 11, the absence of clinical features of NF-1 and their gastric localisation effectively excludes NF-1 as the possible aetiology. In patients with NF-1, GISTs and their precursors commonly present as multifocal gross or microscopic lesions with a marked predilection for the small bowel, but most importantly, they lack activating *c-KIT* and *PDGFRA* mutations [8].

The findings of ICC hyperplasia may explain the development of multiple GISTs in some conditions, possibly because ICC hyperplasia represents a preneoplasic lesion [17]. It has been demonstrated that multifocal sporadic GISTs of the stomach have distinct clonal origins, as individual tumours in the same patient present with different *KIT* or *PGDFRA* mutations [18,19]. However, we could not identify this in our case. Agaimy et al.further suggested the existence of distinct subsets of interstitial cells of Cajal with a higher propensity for different somatic KIT exon 11 mutations [19].

The maximum dimension of the larger GIST was estimated to be <5 cm with a mitotic index of <5 per 50HPF. For gastric GISTs, according to NCCN criteria, this should correspond to a 1.9% risk of progressive disease during long-term follow up and a very low risk of metastasis [20]. However, the presence of ICC hyperplasia, the proximity of the GIST 'tumorlet' to the resection margin and the fragmentation of the tumour during resection might increase the risk of progressive disease and thus justify a more attentive follow up.

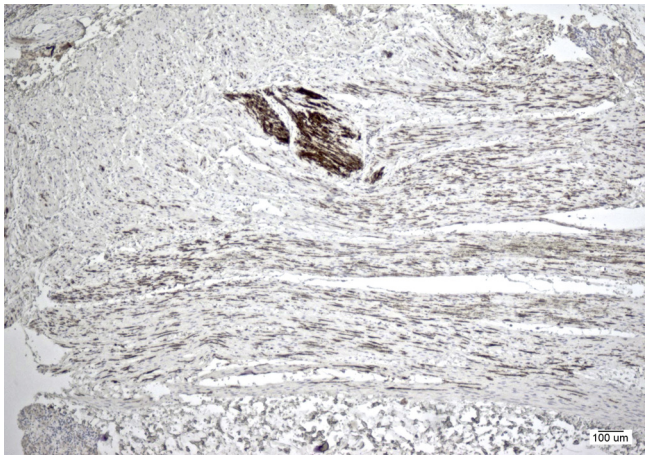

Fig. 4. Microscopic focus of GIST ('tumorlet') away from the main tumour and adjacent to the hyperplasia segment stained with DOG1.

4. Conclusion

In summary, we describe a diffuse form of sporadic ICC hyperplasia showing a very subtle infiltration of the muscularis propria with multifocal GISTs, mimicking diffuse ICC hyperplasia in hereditary GIST syndromes. Detection of somatic *c-KIT* exon 11 mutation ruled out a hereditary disorder.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest

None.

Authors contribution

Dr. Mafalda Costa Neves—Data collection; data interpretation; writing the paper.

Professor Gordon Stamp—Study concept; review of manuscript; pathology, immunohistochemistry and genetic study of the specimen.

Mr. Satvinder Mudan—Study concept, review of manuscript.

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Guarantors

Dr. Mafalda Costa Neves.
Mr. Satvinder Mudan.

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