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REVIEW

Small and microscopically detected gastrointestinal stromal tumours: an overview

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Summary

Small or microscopic gastrointestinal stromal tumours (GISTs) have been the focus of recent publications. These lesions may accompany clinically overt GISTs or be found incidentally in resection specimens for gastro-oesophageal malignancies. While the majority of cases consist of single lesions, approximately 30% may be multiple (usually two or three such lesions). Several appellations have been employed to describe these small GISTs: minute GISTs, GIST tumourlets, interstitial cell of Cajal (ICC) hyperplasia, microscopic GISTs, minimal GISTs, and sclerosing stromal tumourlets. As such, there has been no uniformity in terms of the size of these small or microscopic lesions with tumours as small as 0.2 mm and those up to 10 mm, all falling within the remit of microscopic or minute GISTs. These lesions have a predilection for the gastro-oesophageal junction and occur slightly more frequently in the proximal stomach. They are typified by spindle-shaped cells set within a hyalinised stroma which also shows calcification. Even the smallest lesion has been shown to harbour mutations of the *c-kit* gene. They are biologically indolent, and the majority of lesions appear to remain small and/or show evidence of involution. However, it is possible that some are the precursors of clinically significant GISTs.

Key words: GIST, GIST tumourlet, microscopic GIST, interstitial cell of Cajal, c-kit, CD117.

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INTRODUCTION

With the demonstration of gain of function mutations in the *c-kit* gene located on chromosome 4q11–12 by Hirota *et al.*, mesenchymal tumours of the gastrointestinal tract have undergone a nosological refinement.[1] Thus, based on the *c-kit* mutations, a distinct, well-defined subset of mesenchymal tumours called gastrointestinal stromal tumours (GISTs) have emerged. Miettinen and Lasota have defined GISTs as 'specific c-kit (CD117)-positive and, *c-kit* or *PDGFRA* mutation-driven mesenchymal tumors of the gastrointestinal tract with a set of characteristic histological features including spindle cell, epithelioid and rarely, pleomorphic morphology'.[2] The clinically apparent and symptomatic GISTs have received much attention, especially with the advent of targeted therapy with imatinib mesylate and more recent analogues. Over the last decade, the histogenetic, morphological, immunophenotypical, and, most importantly, molecular and genetic features of GISTs have become increasingly elucidated. Of late, syndromic and familial forms GIST have been identified, and these account for less than 5% of all cases.[2] A putative precursor lesion, hyperplasia of the interstitial cells of Cajal (ICC), has accompanied these inherited forms of GIST. Less commonly, ICC hyperplasia has been encountered in the non-familial and non-syndromic (that is, sporadic) setting.

Two recent studies have focused on sporadic interstitial cell of Cajal (ICC) hyperplasia and so-called minute sclerosing stromal tumours or GIST tumourlets of the stomach, respectively.[3,4] In addition, so-called 'seedling' mesenchymal tumours of the oesophago-gastric region, including incidental GISTs, have also been evaluated recently.[5]

Thus, there is an increasing awareness, detection, and recognition of small, incidental, sometimes multiple, spindle cell lesions in the gastro-oesophageal area that may or may not be associated with clinically apparent GISTs. Several terms have been applied to small GISTs of varying size (range 0.2–10.0 mm). The purpose of this paper is to present an overview of the major studies examining such small GISTs, document their key features, highlight the different terms used to describe similar lesions, and reflect on their significance.

HISTOLOGICAL FEATURES

These small GISTs are located within the muscularis propria and may occur within either the inner circular or outer longitudinal layer (Fig. 1). They are characterised by a spindle cell phenotype often with prominent hyalinisation and calcification (Fig. 2). They are exquisitely positive for CD34 (Fig. 3a) and CD117 (Fig. 3b). The resident smooth muscle fibres of the muscularis propria can sometimes be entrapped within the proliferating ICC. There are no hypercellular foci, mitoses or foci of necrosis. So-called ICC hyperplasia may be diffuse or nodular (Fig. 4). Distinction of the nodular form of ICC hyperplasia from a small or microscopic GIST is extremely difficult.

INCIDENCE

While several reviews on GISTs over the years have mentioned the occurrence of small GISTs, it is only recently that a systematic search for and analysis of such lesions have been undertaken.

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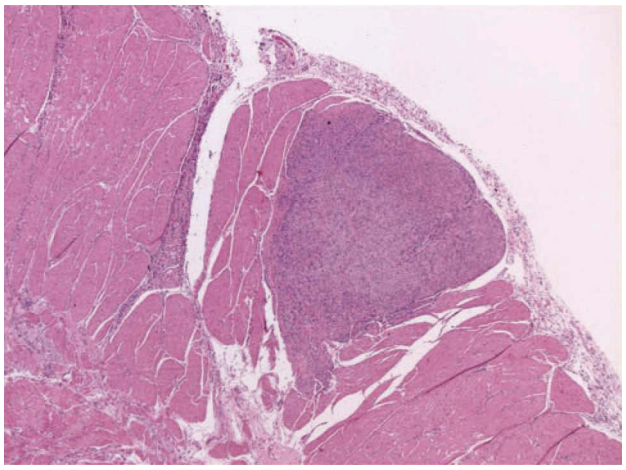

FIG. 1 GIST tumourlet within the outer longitudinal layer of the muscularis propria of the oesophagus.

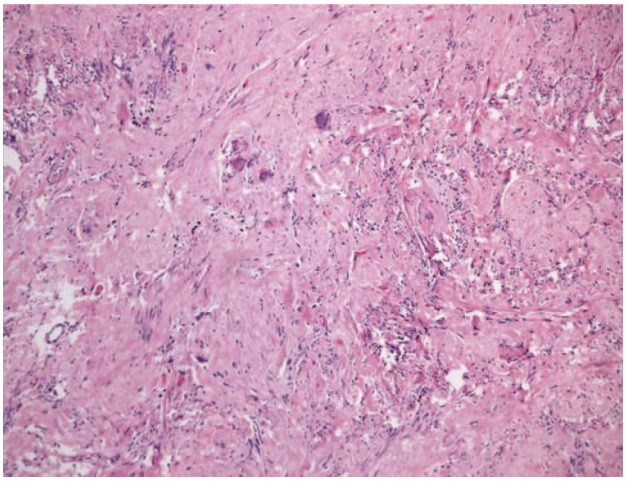

FIG. 2 GIST tumourlets characterised by a proliferation of spindle cells with stromal hyalinisation and calcification. There is no evidence of hypercellularity or cytological atypia.

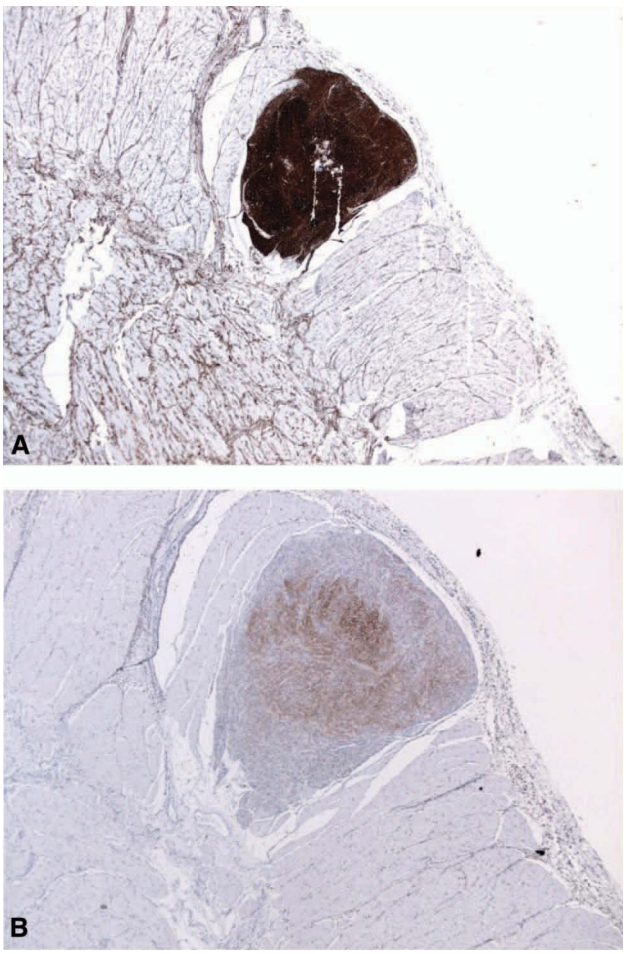

FIG. 3 (A,B) Lesions strongly positive for CD34 (A) and also showing immunoreactivity for CD117 (B).

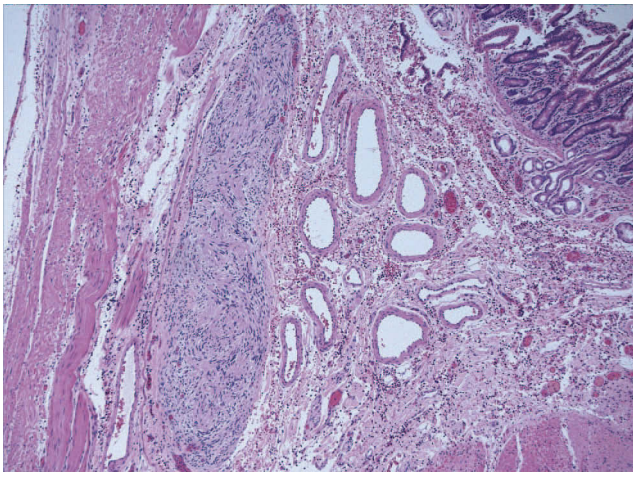

FIG. 4 Circumscribed aggregate of interstitial cell of Cajal hyperplasia within the submucosa. This lesion is composed of a nodular or rounded aggregate of spindle shaped cells and closely simulates a GIST tumourlet.

The paper by Agaimy *et al*. focused on grossly observed, minute sclerosing GISTs that were found in the stomach after careful inspection and palpation.[4] Forty-three GIST tumourlets were identified in 35 autopsy cases, with five cases having multiple lesions (2–5 GIST tumourlets). Of the surgical cases, two of 22 cases had multiple lesions. The lesions tended to occur in the body and fundus of the stomach in patients of either gender ranging in age from 44 to 84 years (mean 70 years), ranging from 2 to 10 mm (mean 5 mm) in size, and were subserosal with variable involvement of the muscularis propria. All cases were composed of spindle cells and devoid of an epithelioid cell component, and calcification was present in the majority of cases.[4]

Kawanowa *et al*. examined 100 total gastrectomy specimens, sectioned at 5 mm intervals.[6] Fifty microscopic GISTs were noted in 35 cases; 45 were located in the proximal stomach, including the oesophago-gastric junction.[6] The lesions encountered ranged in size from 0.2 to 4.0 mm, with a mean size of 1.5 mm. Of the 35 cases containing microscopic GISTs, 12 had multiple lesions: nine cases had two lesions, and three stomachs had three minute GISTs.[6]