Clinical Imaging 37 (2013) 821–829

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: http://www.clinicalimaging.org

Review articles

Gastrointestinal stromal tumors (GIST): lesser known facts

Kevin N. O'Regan [a], Atul B. Shinagare [b], Sachin S. Saboo [b], Nikhil H. Ramaiya [b,c], Jyothi P. Jagannathan [b,c], Sree Harsha Tirumani [b,c,*]

[a] Department of Radiology, Cork University Hospital, Wilton, Cork, Ireland
[b] Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115
[c] Department of Imaging, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, Boston, MA 02215

ARTICLE INFO

Article history:
Received 23 March 2013
Accepted 16 April 2013

Keywords:
Gastrointestinal stromal tumor
Tumor biology
Molecular classification
Atypical metastases
Syndromes associated with GIST

ABSTRACT

In an era of molecular targeted therapy, patients with advanced gastrointestinal stromal tumor (GIST) are living longer and are often followed with imaging. Therefore, it is important for the radiologists to be aware of the atypical subtypes of GIST, implications of molecular makeup, its behavior, and the uncommon metastatic sites. The aim of this pictorial review is to illustrate the lesser-known aspects of GIST including histological and molecular classifications, syndromes associated with GIST, and uncommon metastatic sites.

1. Introduction

Gastrointestinal stromal tumor (GIST) is the commonest mesenchymal tumor of the gastrointestinal tract [1]. GIST arises from the interstitial cells of Cajal and is characterized by the presence of activating mutations in the *KIT* and platelet-derived growth factor receptor (*PDGFR*) proto-oncogenes in approximately 85–95% of cases [1,2]. The typical imaging features of GIST have been well described in the literature, including presentation often with large, heterogeneous masses, in most cases arising from the stomach or small intestine and with a propensity for metastasis to the liver and peritoneum [1,3]. The purpose of this pictorial essay is to illustrate the lesser-known aspects of histological and molecular classifications, atypical metastatic patterns, and syndromes associated with GIST with an emphasis on their imaging features.

2. Histologic classification of GIST

There are three main subtypes of GIST based on histological appearance: spindle cell (70%), epithelioid (20%), and mixed (10%) [2]. The spindle cell subtype presents most often as a large, heterogeneous, enhancing mass arising from the stomach or small intestine. On computed tomography (CT), these tumors often demonstrate central hypodensity with a peripheral enhancing soft tissue component [3]. These tumors harbor the characteristic *KIT* and/or *PDGFRA* mutations in the majority of cases and most commonly arise in adults in their fifth and sixth decades [2,4]. As a result of its favorable molecular characteristics, spindle cell type typically responds well to imatinib mesylate (Gleevec®, ST1571, Novartis Pharmaceuticals, Basel, Switzerland) therapy, often with a decrease in tumor density on CT and has a better overall prognosis (Fig. 1). The less common epithelioid subtype usually arises in the stomach and occurs most frequently in young, female patients [2,3]. This subtype often lacks the characteristic *KIT* and *PDGFRA* mutations and metastasizes to lymph nodes, a phenomenon rarely seen in spindle cell type (Fig. 2).

3. Molecular classification of GIST

The discovery of the activating *KIT* and *PDGFRA* mutations in GIST led to a revolution in the treatment of this disease due to the introduction of imatinib therapy, which inhibits the activation of both receptors (Fig. 3). Treatment resistance in *KIT*-mutated GIST does occur, however, and may be either primary (<6 months of starting treatment) (Fig. 4) or secondary (> 6 months) (Fig. 5). Different types of *KIT* mutation have been shown to predict tumor response to tyrosine kinase inhibition. Most *KIT* mutations in GIST affect exon 11 (75%) and are associated with a favorable response to imatinib [1,5] (Fig. 3). However, in a subset of patients, mutations affecting exon 9 occur, which are mostly encountered in nongastric GISTs, especially those arising from the small intestine, are associated with a decreased likelihood of response to imatinib therapy, and have shorter progression-free and overall survival [5] (Fig. 4). However, high-dose imatinib or sunitinib malate (Sutent®; Pfizer, New York, NY, USA), a multiple tyrosine kinase inhibitor, have been shown to be

* Corresponding author. Tel.: +1-617-632-6312; fax: +1-617-582-8574.
E-mail address: stirumani@partners.org (S.H. Tirumani).

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http://dx.doi.org/10.1016/j.clinimag.2013.04.005

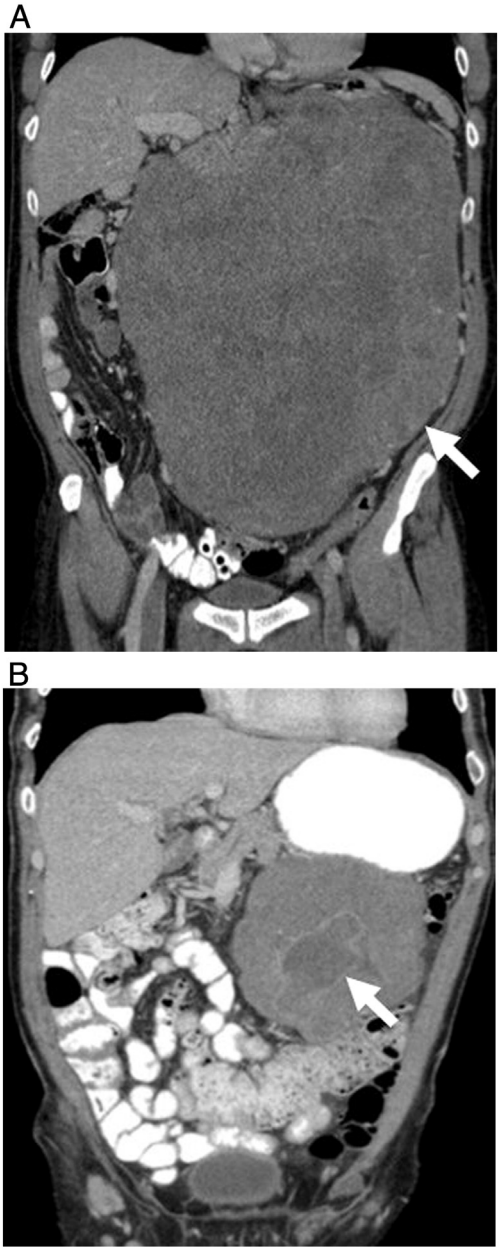

Fig. 1. Sixty-seven-year-old man with spindle cell GIST. (A) Coronal contrast-enhanced CT (CECT) shows a large heterogenerous mass occupying most of the left hemiabdomen (arrow); (B) The mass has markedly decreased in size after 2 months of imatinib treatment, with development of central low attenuation area (arrow).

effective in these patients (Fig. 4) [6]. Though two thirds of *PDGFRA* mutant GISTs show favourable response to imatinib, the exon 18 D842V mutation, which is the most common *PDGFRA* mutation, is resistant to imatinib.

Tumors without any mutations in *KIT* or *PDGFRA* exons are classified as wild-type (WT) genotypes and are also more resistant to imatinib therapy [5]. WT GISTs in up to 10% of cases are associated with mutations in *BRAF* exon 15 (V600E), and these *BRAF*-mutant GISTs have the predisposition to occur in the small bowel [7]. Patients who develop resistance or those intolerant to imatinib can be treated with sunitinib [8,9] (Fig. 5). Interestingly, patients with exon 9 or WT *KIT* mutations show greater benefit from treatment with sunitinib than those with exon 11 mutation [10]. Secondary resistance to imatinib is associated with secondary *KIT* kinase mutations, amplification of *KIT*/*PDGFRA*, or mutations in other tyrosine kinases [11]. Secondary mutations in *KIT* kinase involve either the exons 13 and 14

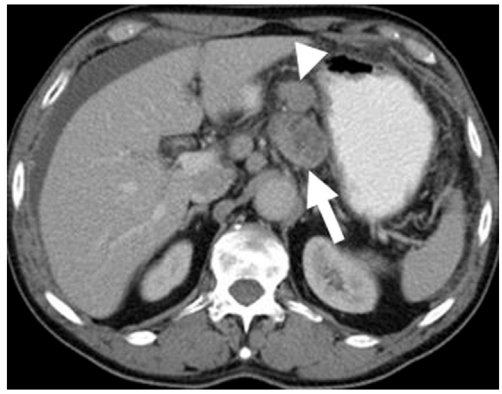

Fig. 2. Thirty-three-year-old woman with epithelioid GIST. Axial CECT shows a heterogeneous perigastric mass (arrow) with adjacent pathologically proven involved lymph node (arrowhead).

(ATP-binding pocket) or the exons 17 and 18 (kinase activation loop) [2]. Heterologous rhabdomyoblastic (skeletal muscle) differentiation, a rare form of secondary resistance, occurs in GISTs treated with imatinib and causes loss of *KIT* expression [12].

4. Pediatric GIST

Pediatric GIST are rare (1% of all GIST), occur most often in the second decade of life, typically arise in the stomach in female patients, and often occur as multifocal tumors with a multinodular growth

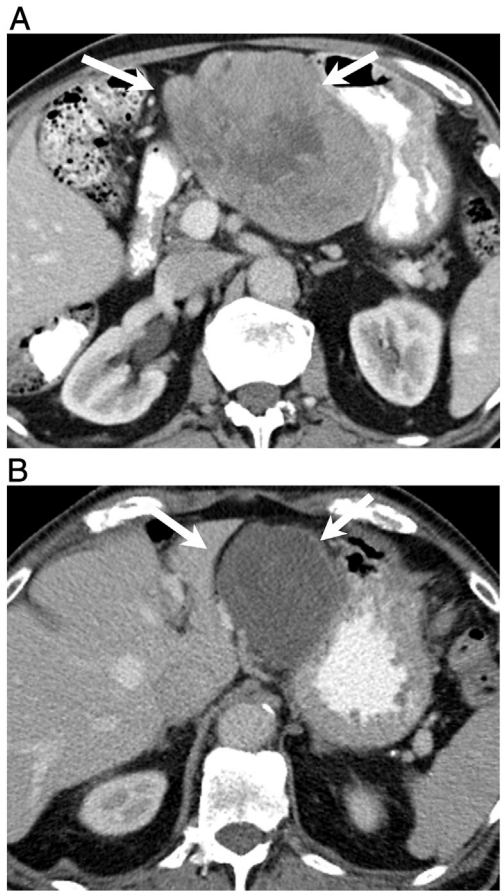

Fig. 3. Eighty-six-year-old man with GIST with exon 11 mutation. (A) Axial CECT shows a large heterogeneous perigastric soft tissue mass (arrows); (B) CECT after 12 months of imatinib therapy shows marked decrease in size and attenuation of the perigastric mass (arrows), indicative of treatment response.