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Review

Resistance to treatment in gastrointestinal stromal tumours: What radiologists should know

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Gastrointestinal stromal tumour resistance to treatment with imatinib occurs due to pre-existing or acquired mutations. Computed tomography and positron-emission tomography play an essential role in prompt recognition of resistance to treatment. Primary resistance to treatment, which is encountered in the first 6 months of treatment, is associated with specific mutations. Imaging of these tumours shows no anatomical or metabolic response to treatment. Secondary resistance to treatment, which develops after an initial response, is associated with a variety of mutations acquired after the start of treatment. Imaging findings of secondary resistance are of disease progression.

Introduction

Gastrointestinal stromal tumours (GISTs) constitute less than 1% of all GI tumours, but with an annual incidence of 15 cases per million in the UK, GISTs are still the most common mesenchymal tumours of the GI tract.[1] Considered to be smooth muscle tumours until the 1990s, GISTs are now known to be derived from interstitial cells of Cajal (the pacemaker cells of the GI tract) or their precursors.[2] The characteristic feature in the pathogenesis of GISTs is the presence of activating mutations of the gene encoding the receptor tyrosine kinase (RTK) KIT. GISTs are inherently resistant to conventional chemotherapy and radiotherapy, and therefore, had a poor prognosis until the development of imatinib mesylate (Glivec®, Gleevec®, Novartis, Basel, Switzerland), which is a RTK inhibitor. Imatinib has dramatic efficacy in advanced GIST and was approved by the United States Food and Drug Administration (US FDA) and European Union in 2002 as the first line of treatment in patients with such tumours. Nevertheless, a subset of GISTs are inherently resistant to imatinib as they harbour different kinds of mutations.[3] Additionally, GISTs may develop secondary resistance to imatinib during the course of treatment.[4] Sunitinib malate (Sutent®, Pfizer Oncology, New York, USA), another tyrosine kinase inhibitor has shown efficacy in imatinib-resistant GIST and was approved by the US FDA in 2006 as a second-line agent for treating imatinib-resistant GIST. Response to sunitinib is also temporary as most patients develop resistance in less than 1 year due to secondary mutations.[5,6] Understanding the molecular basis of these resistance patterns in the past decade and the collaboration between radiologists, pathologists, and oncologists has played a major role in the evolution of the treatment of GISTs and has enabled the development of new treatment strategies. The aim of this article is to provide a comprehensive review of the mutations that may cause resistance to treatment encountered in GISTs with an emphasis on the role of imaging in guiding the management.

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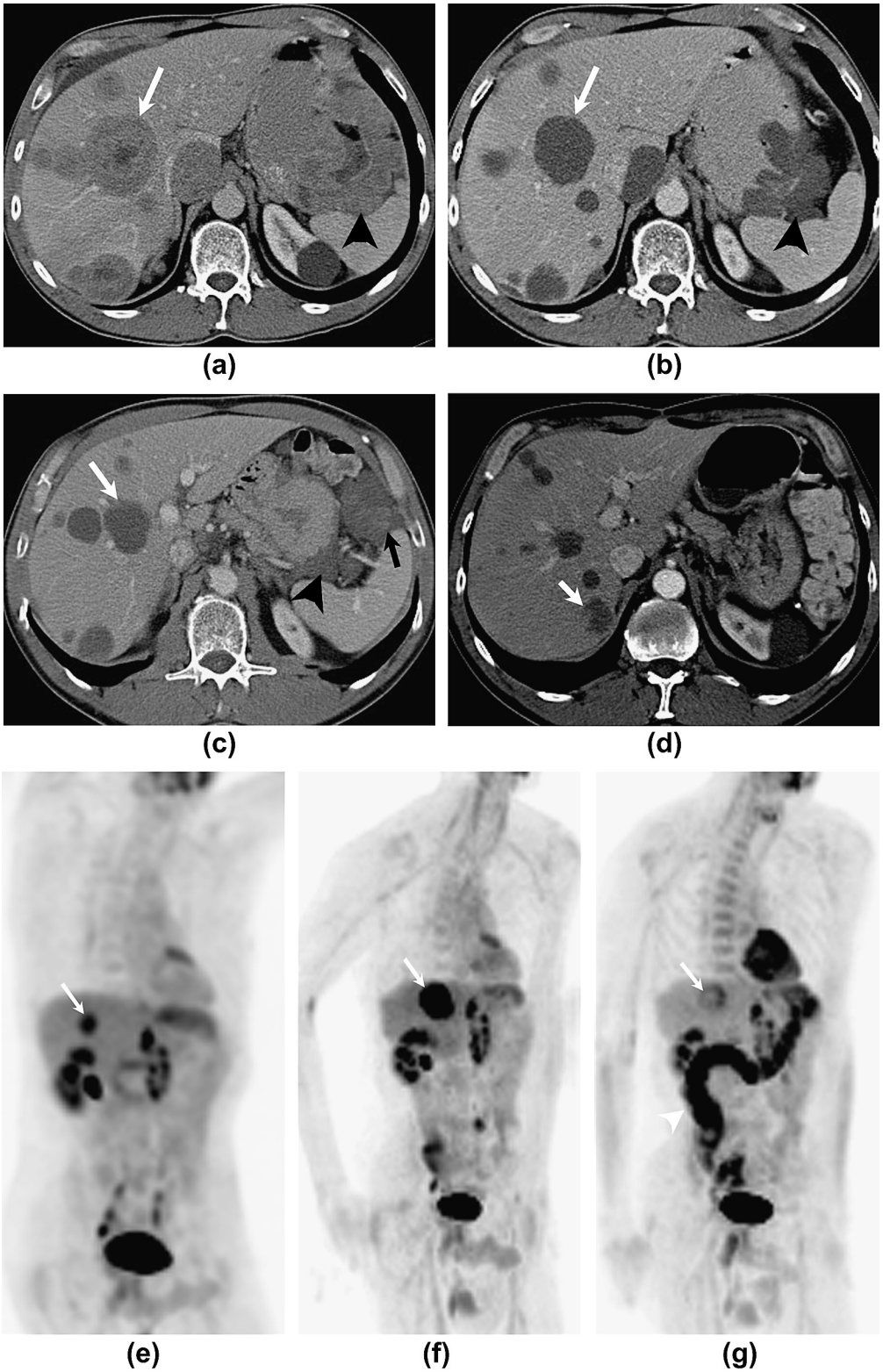

Figure 1 A 62-year-old man with hepatic and peritoneal metastases from GIST treated with imatinib. (a) Axial contrast-enhanced CT image obtained at baseline demonstrates an exophytic gastric tumour with central necrosis (black arrowhead) and multiple heterogeneous hepatic metastases (white arrow). Biopsy of the hepatic metastasis revealed metastatic GIST with *KIT* exon 11 mutations. The patient was treated with conventional dose of imatinib. (b) Axial contrast-enhanced CT image obtained 1 month after start of treatment demonstrates typical response to therapy, with homogeneously decreased density and enhancement of the primary gastric mass (black arrowhead) and hepatic (white arrow) metastases. (c) Follow-up contrast-enhanced CT image obtained 8 months later during the course of imatinib treatment reveals nodular areas of increased density in a peritoneal deposit (black arrow) consistent with disease progression due to secondary resistance. The hepatic metastases (white arrow) and the primary gastric mass (black arrowhead) show continued response. Patient underwent surgical resection of the residual