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Case Report

Massive Multifocal Familial GIST: A Case Report

Samuel R Thomson, Su Ang and Steven Craig*

Department of Surgery, Shoalhaven District Memorial Hospital, Illawarra Shoalhaven Local Health District, New South Wales, Australia

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ABSTRACT

Gastrointestinal stromal tumors (GIST) are uncommon mesenchymal neoplasms of the gastrointestinal tract. The majority of GISTs are the result of sporadic mutations, most commonly of the *KIT* proto-oncogene. Germline mutations account for 5% of GISTs and result in rare familial syndromes. We present a 66-year-old male with a family history of GIST who presented with mild abdominal pain and was found to have a massive, multifocal GIST. The main tumor was resected via laparotomy and the weight was found over 2 kg. He was commenced on adjuvant therapy with imatinib and will be closely monitored. Familial GISTs tend to be larger, multifocal and diagnosed at a younger age. Familial GISTs are extremely rare conditions. There is little to no evidence on the long-term outcomes of treatment on which to base management decisions.

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Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms which usually occur in the stomach (56%) and small bowel (32%). The incidence of GIST is uncommon, with most studies reporting an incidence between 10-15 cases per million per year [1, 2]. The majority of GISTs are the result of sporadic mutations to the *KIT* proto-oncogene which accounts for >90% of cases [3]. However, there are rare reports of inherited germline mutations to these genes resulting in familial GIST syndromes. These syndromes include primary familial GIST syndrome, Carney-Stratakis syndrome, and neurofibromatosis type 1 [4]. Familial GIST was first described in 1998, and since then, only 51 affected families have been reported in the literature [5, 6]. Here we present a patient who has a second-generation, familial GIST with a massive, multifocal tumor burden.

Case Report

A 66-year-old male presented to his general practitioner with a 6-week history of progressive intermittent left upper quadrant abdominal pain, which was cramping in nature and exacerbated by stretching and movements. He was otherwise well and denied any other constitutional symptoms. He had no significant medical or surgical history. His family history was significant in that his father had undergone resection of an open GIST resection at an age of 80, though no further details were available at the time. On clinical examination, there was a palpable mass extending from the left hypochondrium to the left flank, which was firm, slightly tender and estimated to be 10cm x 15cm in size. Computed tomography (CT) of the abdomen and pelvis demonstrated a large left-sided abdominal mass (182mm x 95mm x 148mm) and a calcific mass in the right lower quadrant (20mm x 32mm x 30mm) and multiple omental nodules (Figure 1).

*Correspondence to: Dr. Steven Craig, Department of Surgery, Shoalhaven District Memorial Hospital, Illawarra Shoalhaven Local Health District, New South Wales, Australia; E-mail: steven.craig@health.nsw.gov.au

Figure 1: CT imaging of the lesion, axial tumor dimensions 183 x 96mm, coronal tumor dimensions 149mm.

Figure 2: Resected massive intra-peritoneal gastrointestinal stromal tumor weighing 2070 grams.

Figure 3: Intraoperative photo of the gastrointestinal stromal tumor prior to resection.

The patient proceeded to have a diagnostic laparoscopy for the purpose of obtaining a tissue diagnosis. At surgery, a large, bloody and friable mass was found in the left upper abdomen with multiple adhesions. There was a moderate volume of fresh and old intra-abdominal blood,

and a decision was made to convert to open laparotomy to control the bleeding. The largest tumor was resected from the greater omentum and small bowel using blunt and LigaSure dissection, weighing 2.07 kg (Figure 2). There were innumerable further masses arising from the mesenteric border of the small bowel and mesentery, as well several larger exophytic masses involving the anti-mesenteric proximal jejunum and omentum (Figure 3). Complete resection was not possible given the vast number of tumors, so the operation was ceased. There were no perioperative complications. Macroscopically, the large, resected tumor weighed 2070 grams and was multifocal, made up of multiple nodules of variable size, colour and consistency. The cut surface of the tumor was mostly homogenous pale pink to tan with areas of hemorrhage (Figure 4A).

Histology showed fibroadipose tissue with extensive infiltration of a mesenchymal neoplasm, predominately epithelioid morphology with some spindle cells, arranged in large solid sheets, nodules and multiple lobules. Areas of necrosis were also noted. The mitotic count was variable, up to 40 per 5mm² and the Ki-67 index was 40%. Immunohistochemistry stains were CD117+ (*KIT*+), DOG1+, CAM5.2-, SOX10-, S100-, desmin-, consistent with a GIST (Figures 4B-4D). Further staining was performed, showing *SDHB*+ and *SDHA*+ which excluded a diagnosis of *SDH* deficient GIST. The pathologic stage was pT4pN0 and was categorised as high risk. He was commenced on adjuvant therapy with imatinib postoperatively and regular clinical review.

Figure 4: A) Macroscopic appearance of cut surface of tumor specimen, B) micrograph demonstrating multinodular architecture, C) micrograph demonstrating predominantly epithelioid cell morphology, D) CD117 (*KIT*) immunohistochemical stain.

Discussion

We present a case of *KIT* positive familial GIST with a massive, multifocal tumor burden. Astoundingly, the patient presented with only mild abdominal pain in spite of the large volume of disease and intra-abdominal bleeding found on laparoscopy. The vast majority of GISTs present with a solitary, intra-luminal tumor. Thus, our case is an atypical presentation of an extremely rare familial syndrome in which there were largely exophytic, intra-peritoneal tumors. Around 50% of GISTs present asymptotically and are incidentally diagnosed on imaging, endoscopy or during surgery [7]. Those that are symptomatic generally have gastrointestinal bleeding or anaemia, with a smaller proportion having abdominal pain depending on the tumor location [8]. Symptoms and imaging findings are always non-specific for diagnosis, and histopathology and immunohistochemical markers are essential. The most specific immunohistochemical marker for GIST is CD117 or *KIT*. Approximately 95% of GISTs are *KIT* positive, as was seen in the presented case [9]. Of the 51 familial GISTs reported in the literature, 46 had mutations in the *KIT* proto-oncogene [6].

Familial GISTs tend to present at an earlier age than sporadic GISTs, with a median age of 46 years, which is nearly a decade earlier than sporadic GISTs [1, 6]. Our patient presented at 66-years-old, albeit with a significant tumor burden with multifocal GISTs suggestive of long-standing disease. Multifocality is much more prevalent in familial GISTs [10]. Familial GIST is also associated with larger tumors. Caterino *et al.* looked at 47 consecutive patients undergoing resection for primary GISTs and showed the mean maximum tumor diameter from their 47 cases was 7.4 cm [7]. In our reported case, we encountered an extremely large tumor measuring over 20 cm in diameter. Given these different characteristics between sporadic and familial GISTs, we recommended that familial GIST should be strongly suspected in any patient with a family history of GIST tumor, who presents at age <50 years, or with multifocal and large tumors.

There is very little evidence regarding the long-term treatment and outcomes of patients with familial GISTs, given the rarity of cases, and

as such, it is difficult to make strong treatment recommendations. Most treatment decisions are based on evidence for the treatment of sporadic GISTs. The accepted gold standard for sporadic GISTs is surgical excision aiming for complete resection, with targeted adjuvant chemotherapy in the form of the tyrosine kinase inhibitor imatinib [11]. In this case, complete resection was not possible due to the disease extent; however, surgery was still necessary for tissue diagnosis as well as control of the large and bleeding primary tumor. Following surgery, the patient has been commenced on imatinib for disease control, with further imaging to assess progress every 6 months.

This case highlights a rare case of familial GIST presenting with remarkably mild symptoms despite massive and multifocal tumor burden. Management is challenging due to a lack of literature regarding familial GISTs and highlights the need for further reporting, particularly on long-term outcomes.

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