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Review

Exploring the Genetic and Therapeutic Landscape of Gastrointestinal Stromal Tumors: A Case of Successful Intervention in Metastatic Disease

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Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors arising from the interstitial cells of Cajal. Originally thought to be leiomyosarcomas, these tumors are traditionally resistant to chemotherapy and radiation therapy. Molecular studies have identified the gene mutations that cause these masses to proliferate. The KIT proto-oncogene and PDGFRA mutations have been successfully implicated as the insults leading to disease. We present a 54 year old male, whose tumor was very aggressive yet multi-modality therapy did show an excellent response. Discovered incidentally while he was undergoing a sigmoid colostomy for benign disease, the patient had evidence of metastatic GIST disease. We utilized radiology, pathology and immunohistochemistry to provide a definitive diagnosis. Radiology was extremely useful in identifying disease and possible metastases. Furthermore the use of PET scans, particularly PET/CT allows clinicians to monitor and tailor therapy. Successful management of GISTs involves medical and surgical therapy. Imatinib mesylate is a drug used to inhibit the production of the KIT proto-oncogene. Coupled with surgery, this combination holds promise in successful management and possible eradication of the disease.

Key words: Gastrointestinal stromal tumor, PET scan, Imatinib, gene therapy, small bowel obstruction.

INTRODUCTION

A 54 year old male with a history of recurrent diverticulitis presented for surgical evaluation and management for his disease process. His past history was significant for a right hemicolectomy for carcinoma 10 years previously. An elective sigmoid resection was scheduled and upon entry into the abdominal cavity, several suspicious peritoneal nodules were seen on the anterior abdominal wall. Biopsy and frozen section demonstrated indurated tissue with fatty necrosis. The sigmoid colectomy was completed without incident.

Further abdominal exploration identified a mid-jejunal "tennis ball" size (approximately 9 cm in diameter) mass as the only other abonormality. This was resected en-bloc and sent for pathological analysis.

Pathological analysis demonstrated multiple sigmoid diverticula with diverticulitis, jejunal malignant gastro-intestinal stromal tumor (GIST), 5.3 cm in diameter and metastatic peritoneal GIST. Retrospective review of the abdominal/pelvic computed tomography (CT) scans that had been obtained for diverticulitis failed to show any intra-abdominal masses. Following surgery, the patient's clinical course was uncomplicated with plans to begin imatinib mesylate (STI571, Glivec, Gleevac, Novartis) within 4 - 6 weeks postoperatively.

One month postoperatively, cancer staging with CT

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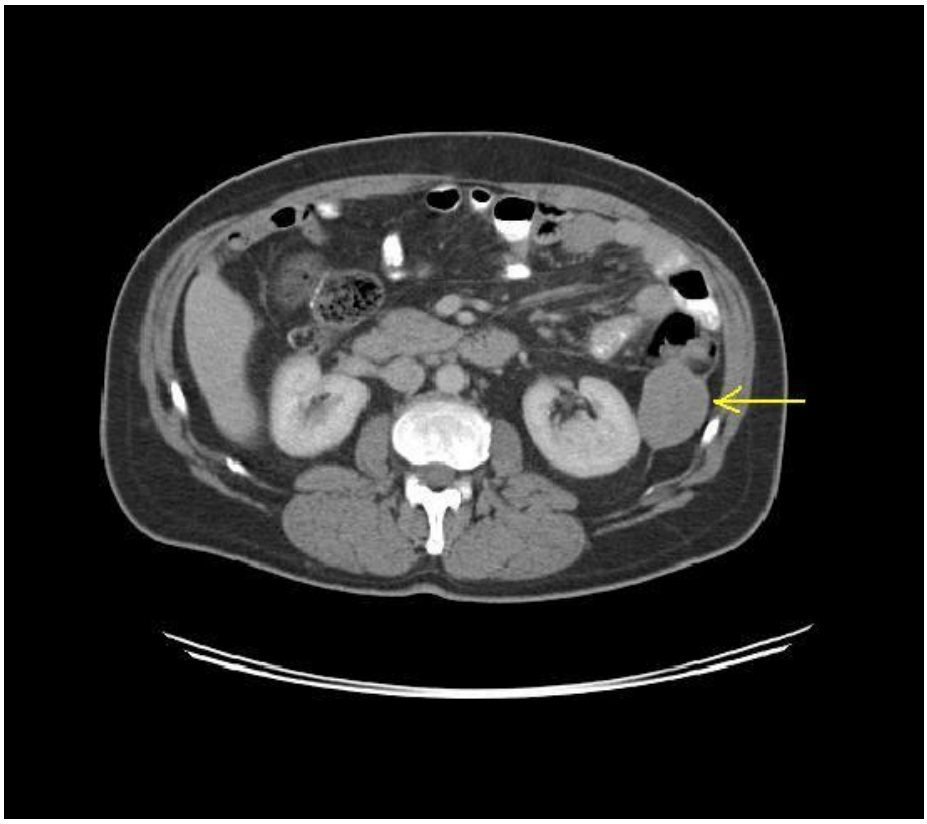

Figure 1. Contrast enhanced CT scan of the abdomen/pelvis in the axial plane showing a mass (arrow) lateral to the kidney and inferior to the spleen. The mass measured 4.8 x 3.6 cm.

scans revealed multiple abdominal masses throughout the peritoneal cavity including an inferior pole of the spleen mass, measuring 4.8 x 3.6 cm (Figure 1). The patient concurrently underwent a Positron Emission Tomography (PET) scan on the same day which confirmed multiple hypermetabolic masses throughout the peritoneal cavity (Figure 2).

Five weeks following surgery and 7 days after his radiological survey, the patient presented to the hospital with abdominal pain, nausea and bouts of vomiting. He was admitted with a tentative diagnosis of partial vs. complete small bowel obstruction. CT imaging, (Figure 3) demonstrated significant interval enlargement of the peritoneal/mesenteric tumor implants. Dilated loops of small bowel were seen without a transition point.

The patient was placed on bowel rest and decompressed using a nasogastric (NG) tube. The decision to start imatinib [imatibnib mesylate (Glivec or Gleevac by Novartis)] immediately was undertaken. The patient showed a remarkable response to imatinib therapy. Over the course of the next 5 days, his nausea subsided and his bowel function started to return. He was discharged 6 days following imatinib therapy.

A CT scan, obtained one month from his previous CT scan and bout of partial small bowel obstruction. (Figure 4) demonstrated stable disease despite his clinical improvement.

BACKGROUND

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that arise in the gastrointestinal tract from the interstitial cells of Cajal (ICC). They are rare with an incidence of 3000 - 6000 cases per year (Fletcher et al., 2002; Tryagvason et al., 2005; Efron, 2008). Originally treated as leiomyosarcomas; these tumors are radically resistant to standard chemotherapy and radiation therapy.

Molecular biology and etiology

Molecular investigations of GIST show mutations within the KIT proto-oncogene and the Platelet Derived Growth Factor Alpha (PDGFRA) gene signaling. The KIT and PDGFRA genes are part of the tyrosine kinase receptor family. Mutations are associated with constitutive activetion and receptor phosphorylation which lead to loss of inhibitory function and excessive proliferation (Sciot

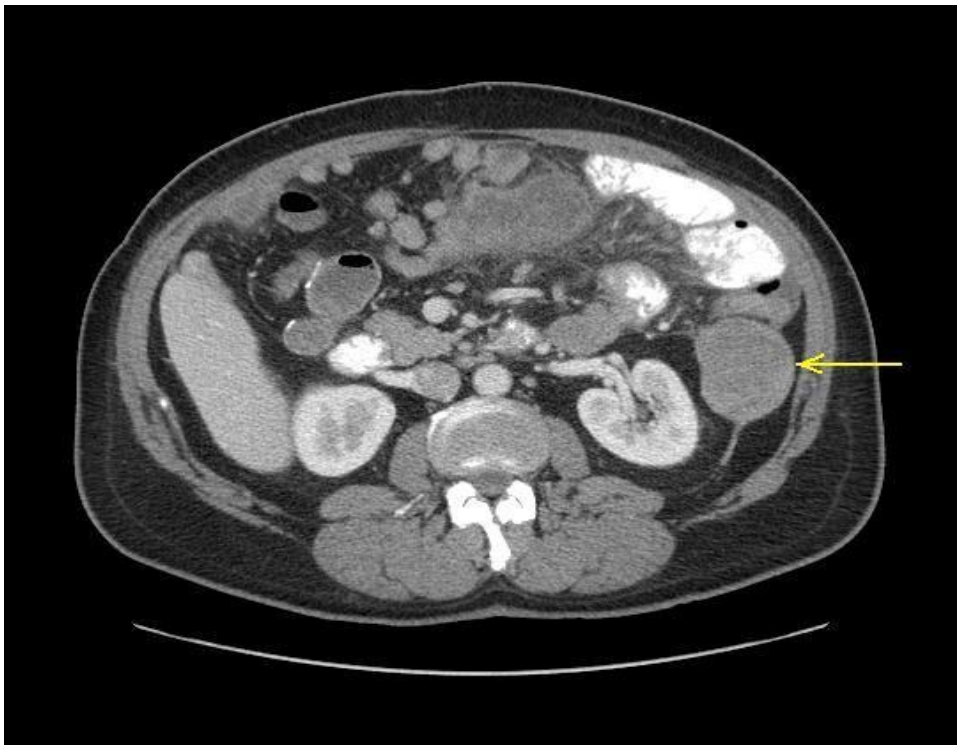

Figure 2. Contrast enhanced CT scan of the abdomen/pelvis in the axial plane depicting the same mass (arrow) increased in size, measuring 5.6 x 4.2 cm.

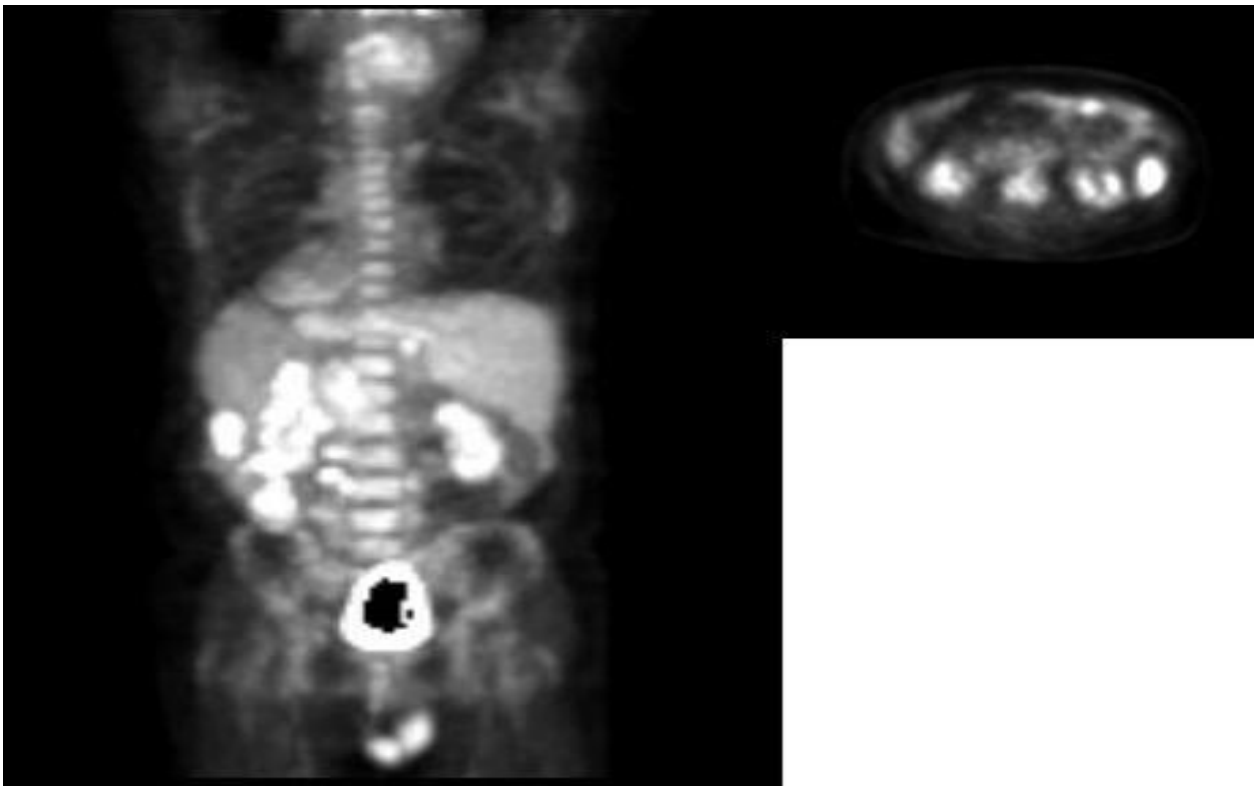

Figure 3. PET Whole Torso imaging, following injection of 14.0 mCi F-18 fluorodeoxyglucose showing multiple intraperitoneal masses, compatible with metastases from GIST. Right: PET/CT axial images depicting multiple intra-abdominal areas of hyperintense uptake representative of metastatic disease.

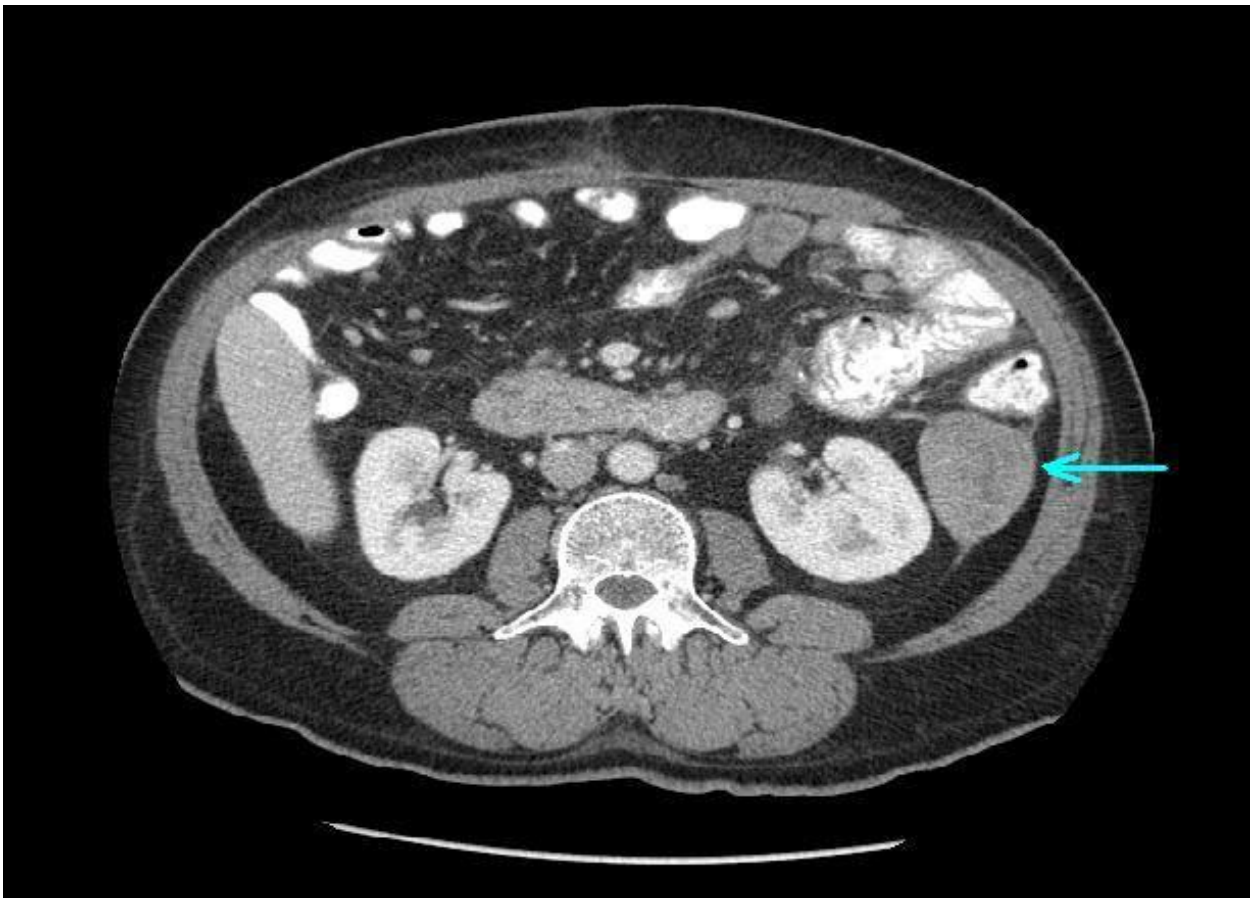

Figure 4. Contrast enhanced CT scan of the abdomen/pelvis in the axial plane. There were several intraperioneal masses, with the largest mass (arrow) approximately the same size when compared to the previous CT images.

and Debiec-Rychter, 2006). This cascade phosphoylates other kinases such as PI3 kinases, STAT and JAK which induce unregulated miotgenesis.

The KIT receptor is crucial in the development of the interstitial cells of Cajal. Furthermore, this receptor is influential in hematopoeisis, gametogenesis and melanogenesis both in embryonal development and following delivery (Huizinga et al., 1995; Maeda et al., 1992; Torihashi et al., 1995; Antonescu, 2008).

In several case series, the triggering factors in GIST development have been correlated to genetic predisposition. Families with GIST predisposition have germ line mutations in the KIT gene on chromosome 4 or PDGFRA gene mutations (Baselga and Arteaga, 2005; Chompret et al., 2004; Maeyama et al., 2001; Chen et al., 2002; Hirota et al., 2000; Isozaki et al., 2000; Robson et al., 2004; O'Riain et al., 2005). A frequent mutational site has been identified in the juxtamembrane domain encoded by exon 11 (Kleinbaum et al., 2008). There are, however, numerous exons implicated in GIST development including exons 9, 13, 17 for the KIT proto- oncogene and exons 12, 14, 18 for PDGFRA mutations (Miselli et al., 2008). Although several reports in the literature have reported a decreasing median age for GIST diagnoses and occurrence, in the familial cohort, it is difficult to determine whether this truly is a product of aggressive and successive genetic mutation or better radiological imaging detecting GIST pathology earlier (Robson et al., 2004; Kleinbaum et al., 2008).

Diagnosis: Clinical presentation

The majority of sporadic GIST lesions arise in the stomach (60%), followed by the small intestine (30%) (Nilsson et al., 2005) . The tumor associated mortality is almost twofold higher when the lesions are located in the small intestine (35% vs. 18% respectively) (Miettinen et al., 2003; Miettinen et al., 2005; Emory et al., 1999). Interestingly familial GISTs have a propensity to arise from the small intestine, or small intestine and stomach, but seldom from the stomach alone (Isozaki et al., 200;Robson et al., 2004; Handra-Luca et al., 2001; Li et al., 2005; Chen et al., 2004). The clinical presentation varies with some patients being completely asymptomatic where the lesions are detected as "incidentalomas" upon

radiological survey for various reasons. Other patients present with marked abdominal pain, signs of obstruction or impressive gastrointestinal bleeding representing diffuse and/or progressive disease.

Diagnosis: Radiological imaging

Computed tomography (CT) scanning is employed in a variety of clinical scenarios and has practically become an extension of the physical exam. GIST lesions are often found as “incidentalomas” or are identified as masses on CT imaging. This radiological modality allows the clinician to survey the intra-thoracic, intra-abdominal and pelvic cavities without invasive procedures. It also allows the patient’s lesions to be measured and monitored once a diagnosis has been established. The objective response to surgical and/or medical manage-ment is measured using several oncologic models and criteria. The Response Evaluation Criteria in Solid Tumors (RECIST) for unilateral tumor measurement or Southwest Oncology Group (SWOG) criteria for bidirec-tional measurement employ CT imaging for evaluation (Holdsworth et al., 2008; Therasse et al., 2000; Green and Weiss, 1992). RECIST criteria require at least a 30% reduction in unidirectional measurement to categorize treatment as rendering a partial response. Concurrently a reduction of > 50% must be achieved to fulfill the require-ments of partial response under the SWOG criteria. Although the measurements are exceedingly accurate using CT imaging, the response rate is attributed solely to size reduction. CT imaging does not have the capability to quantify or qualify a response in metabolic tumor activity.

Positron Emmission Tomography (PET), using fluorine-18 -fluorodeoxyglucose (^{18}FDG), can be used to evaluate the metabolic activity of GIST tumors. Not only does PET identify the lesions appreciated on CT imaging, but attempts to discern metabolic deposits from their biologic activity. Once medical therapy has been implemented, ^{18}FDG-PET has been utilized to measure the tumor response. The response has been reported to occur within 24 h of instituting medical therapy, but usually is better appreciated after a month of treatment (Van den Abbeelle, 2001, 2008).

PET imaging has already been employed as criteria for demonstrating responses to medical therapy. The European Organization for Research and Treatment of Cancer (EORTC) advocated and defined that a 25% reduction in maximum standardized uptake value (SUVmax) would be eligible criteria for a partial response (Holdsworth et al., 2008; Young et al., 1999; Straus and Conti, 1991). A documented change in SUVmax < 2.5 has also been reported to correlate with eventual tumor response (Van den Abbeelle, 2008). Recent studies have also attempted to identify PET activity and CT measure-ment in delineating not only clinical and radiological responses but Time to Treatment Failure (TTF). TTF is defined by objective disease progression, death, or with-drawal of medical therapy due to failure (Holdsworth et al., 2008). Prolonging TTF, obviously, is the goal with the institution of medical therapy, yet identifying which patients benefit most form initial medical therapy remains a challenge.

Holdsworth et al. reported that re-establishing a SUVmax at 3.4 and concurrently establishing a SUVmax reduction by 40%, coupled with no growth on CT ima-ging, better reflected and predicted successful medical therapy (Holdsworth et al., 2008).These criteria further predicted more accurately the TTF period as well. Previous generation PET scanners adequately identified regions of increased metabolic activity however were not precise with measurements of tumor size. With the advent of 18FDG- PET/CT, the compilation of SWOG, RECIST, EORTC can all be incorporated in truly attempting to identify tumors that are responsive to medical therapy. Furthermore, the results at one month time can influence further therapy selection whether it is surgical resection or changing the medical regimen. This combined imaging modality optimizes the evaluation of metabolic activity alongside precise tumor measurements (Antoch et al., 2004).

Diagnosis: Pathology

Pathological analysis of tumor specimens is exceedingly important for establishing a definitive diagnosis and influencing management. Immunohistochemical markers for GIST include CD- 117, which is a product of the KIT proto- oncogene (Blay et al., 2005; Miettinen et al., 2002). CD34 also is involved in immunohistochemistry, used as a marker for dendritic fibroblastic interstitial cells (Tsukuda et al., 2007). It has been reported that up to 4% of GIST cases are KIT (CD117) negative (Medeiros et al., 2004) . Furthermore CD117 is not pathopneumonic for GIST with false positives occurring with other mesenchy-mal neoplasms such as desmoids and leiomyosarcomas (Tornillo and Terracciano, 2006). In spite of these short-comings, immunohistochemistry remains the most accurate method for diagnosing GIST lesions.

Molecular genotyping further influences medical management. Tumors that exhibit KIT exon 11 mutations have a better response to medical therapy with Imatinib. Tumors with KIT exon 9 mutation responded better to higher doses of Imatinib, 800 mg/day versus the standard 400 mg/day (Antonescu, 2008). Genotyping also is im-portant to know, particularly as tumors with KIT (CD117) negative mutations might benefit for different medical therapy, such as Sunitib.

Pathological analysis of GIST is important in determining metabolic activity. The metastatic potential of GIST was established at a 2001 consensus conference demonstrating that tumors greater than 5 cm with a mito-

tic count of > 5 per 50 high power, tumors > 10 cm, or tumors with > 10 mitotic count per 50 HPF were at a higher risk for metastases. Metastases were usually into adjacent organs, the liver and lungs.

Medical therapy of GIST consists of Imatinib mesylate (Glivec, Gleevac Novartis). Imatinib targets KIT and PDGFRA proto-oncogene by completely inhibiting ATP from binding to its respective kinase. This inhibition prevents subsequent phosphorylation and blocks eventual activation of downstream signally pathways (Tornillo and Terracciano, 2006). Unfortunately with prolonged use, GIST can develop resistance to imatinib therapy. Resistance manifests either as primary, complete absence of response, or secondary where patients initially benefit and then develop an attenuated response, generally seen within six months. Secondary resistance is postulated to occur from subsequent mutations of the KIT proto-oncogene, over expression of the KIT gene or possibly even a mutation to an alternative, unidentified kinase (Sciot and Debiec-Rychter, 2006). Interestingly, the distinction between primary resistance and active efficacy can sometimes be blurred initially. Several reports in the literature documented increase in tumor growth with initial Imatinib therapy due to intratumoral hemorrhage (Sciot and Debiec-Rychter, 2006).

Pathological evaluations of GIST responding to Imatinib depict myxohyaline stroma representing induction of apoptotic pathways (Corless et al., 2005) . There is also a component of vascular compromise portrayed by decreased blood flow and blood vessel density within the GIST. This effect is likely attributed to mediation of the PDGFRA in vascular pericytes of tumor vessels (Sciot and Debiec-Rychter, 2006; Bagley et al., 2005; Song et al., 2005). These findings of anti-vascularity have spurred interest in other molecular modulators that hold a greater promise of anti-angiogenic activity. Sunitinib (Sutent, Pfizer) has been employed in patients who exhibit either primary or secondary resistance to Imatinib. Similar to Imatinib, Sunitinib inhibits the tyrosine kinase activity of KIT and PDGFRA but also targets vascular endothelial growth factor receptor (VEGF) tyrosine kinases.

Management: Surgical intervention

Surgical excision for cure remains the goal for GISTs. Obtaining clear margins helps to eradicate the disease process; however, these lesions are often not amenable to surgical excision. Furthermore, following complete excision of gross disease, there is no guarantee of complete eradication of the disease, without the potential of recurrence. Recent trials have attempted neoadjuvant therapy with imatinib followed by surgical excision if amenable. The authors reported a 23.8 month progression- free survival in patients who had responded favorably to medical therapy. They, however, did not report any benefits for debulking metastatic disease and minimal benefit, 3.8 month progression-free, for generalized progressive disease.

The patient presented in this case demonstrated rapid tumor growth within 4 weeks despite surgical resection with minimal residual disease. The partial small bowel obstruction (PSBO) that ensued following his initial surgery, improved quickly with imatinib despite significant change in tumor volume on imaging. Therefore, biologic antineoplastic therapy may be an excellent option in patients with PSBO without obvious surgical indications. Careful evaluation is required to allow early recognition of a complicated SBO; however molecular modulation of GIST may provide a significant benefit as adjuvant or palliative treatment of GIST.

We advocate the use of immunohistochemistry and PET imaging in the diagnosis of GIST. Molecular analysis has gained importance, particularly as it can aid in the prediction of medical therapy (Corless et al., 2005). Although our patient's pathology has yet to me molecularly analyzed, mutations in exon 11, reflect the best response to imatinib therapy (Corless et al., 2004). Given the malignant profile of our patient, however, medical therapy, particularly imatinib, warranted a trial to address the disease process. Early surgical intervention is important in eradication of the disease and for determining the aggressive nature of the tumor; however molecular therapy has and does play a very important role in the maintenance and management of disease survival.

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