Rhabdomyosarcomatous Transformation of a Gastrointestinal Stromal Tumor following Treatment with Imatinib

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1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the alimentary tract. GISTs most commonly affect adults over the age of 50 with a slight male predominance [1]. These neoplasms are believed to arise from the interstitial cells of Cajal and over 80% express CD117 (c-Kit) by immunohistochemistry (IHC) [2]. Characteristically these neoplasms contain activating mutations in KIT, or less commonly platelet derived growth factor receptor alpha (PDGFRA). These genetic alterations result in a gain of function or constitutive activation of the encoded tyrosine kinases [1]. Morphologically, GISTs are composed of spindle, epithelioid, or rarely pleomorphic cells and most commonly also express CD34 and DOG1 antigens by IHC [2, 3]. Interestingly, relatively recent reports of rhabdoid or rhabdomyosarcomatous (RMS) differentiation have been described in these tumors [4–6].

Imatinib, a tyrosine kinase inhibitor (TKI), is the current mainstay of treatment for individuals with unresectable or metastatic disease based on data from Demetri et al. showing sustained objective response in more than half of patients treated [7]. This potential drug response is most efficacious in those tumor harboring exon 11 Kit mutations, while those with exon 9 mutations showed worse prognosis and benefited more from higher-dose therapy [8].

Herein we report a case of metastatic GIST with rhabdomyosarcomatous transformation following treatment with imatinib.

2. Materials and Methods

Surgical specimens were fixed in 10% neutral buffered formalin. Following fixation gross examination was performed and representative sections were embedded in paraffin. Five micron thick hematoxylin and eosin stained sections were created. Immunohistochemistry for CD117 (rabbit monoclonal, Cell Marque, Rocklin, CA), CD34 (clone MY10, BD Biosciences, San Jose, CA), DOG1 (clone K9, Leica Biosystems, Buffalo Grove, IL), desmin (clone DE-R-11, Leica
Biosystems), smooth muscle actin (clone alpha sm-1, Leica Biosystems), myoD1 (clone 5.8A, Dako, Carpinteria, CA), and myogenin (clone F5D, Dako) was performed. Molecular analysis for KIT mutation was performed at an outside laboratory (OHSU, Portland, OR) using DNA extraction and purification of paraffin embedded tumor tissue.

3. Results

3.1. Clinical History. A 47-year-old African American male presented to the emergency department with complaints of right lower quadrant abdominal pain and a 20-pound weight loss over the prior two months. The patient had no significant past medical history or any other symptomatology. Computerized tomography (CT) imaging revealed a 14 cm tumor with possible central necrosis that originated from the posterior gastric wall and extended superiorly to the diaphragm (Figure 1(a)). Additionally, there appeared to be metastases in the right pelvic cavity (5.5 cm) and within a right inguinal hernia (4.5 cm). An endoscopic biopsy of the gastric lesion revealed a spindle cell neoplasm which was strongly and diffusely immunoreactive for CD117, CD34, and DOG1. S-100 protein, smooth muscle actin, desmin, and cyokeratin IHC were negative. The diagnosis of GIST was rendered. The patient was initiated on imatinib 400 mg daily. Initial molecular testing was negative for exon 9 or exon 11 mutations. Two months after initiation of treatment, however, there was radiographic evidence of treatment response with a significant decrease in size of all tumors (Figure 1(b)).

Eight months after initiation of imatinib CT imaging demonstrated tumor regrowth and heterogeneous enhancement at the primary tumor site while other metastatic sites remained stable. The dose of imatinib was subsequently escalated to 800 mg daily (400 mg bid).

Approximately one year after his initial presentation, the patient presented with upper gastrointestinal bleeding and an associated microperforation due to tumor progression (Figure 1(c)). Given concerns for abscess and developing fistula by imaging, a palliative surgical procedure was undertaken and included en bloc resection of the tumor with a total gastrectomy/Roux-en-Y esophagojejunostomy, distal pancreatectomy, splenectomy, left partial hepatectomy, and extended right colectomy.

3.2. Histopathological Diagnosis and Genetic Analysis. The resection revealed a 10.4 × 6.4 × 6.3 cm tumor arising from the stomach and invading into the spleen and pancreas. The bulk of the tumor was composed of pleomorphic, eosinophilic polygonal cells with bizarre nuclei, abundant cytoplasm, and increased mitotic activity (up to 3 mitotic figures per 50 high power fields) (Figure 2(b)). Also observed were areas of marked hyalinization, consistent with treatment effect,
Figure 2: Tumor at the time of en bloc resection. Left panels showing H&E (a, b) and immunophenotype of spindle cell component (a, c, e, g, and i) and right panels showing rhabdomyosarcomatous component (b, d, f, h, and j) as follows: (c, d) c-kit IHC, 200x, (e, f) DOG1 IHC, 200x, (g, h) desmin IHC, 200x, and (i, j) myoD-1, 400x.
4. Discussion

To our knowledge, only 6 cases of rhabdomyosarcomatous dedifferentiation in GISTs have been reported following treatment with TKIs [4, 5]. Heterologous differentiation of the primary tumor (as opposed to the metastases) has only been reported in 1 other case. This is the first report of the exon 11 deletion KV558-559 in this clinical setting.

The rare cases of dedifferentiated tumors have generally demonstrated a more aggressive clinical course, with recurrence and metastases. This stands in contrast to primary GISTs with rhabdoid morphology, which, although also uncommon, have not demonstrated malignant behavior [6, 9].

Based on the small number of previously reported cases, dedifferentiated tumors, as in our case, demonstrate resistance to the currently available TKI therapy. Time to treatment failure in these rare tumors with RMS dedifferentiation ranged from 10 to 24 months [4, 5]. Our patient had only 8 months of stable disease following TKI therapy.

In general, when treatment failure occurs, a unique pattern of disease progression follows, termed a “resistant nodule.” These nodules are seen on imaging as new central or peripheral areas of enhancement within preexisting responding lesions. These imatinib “resistant nodules” appear in about 50% of patients after two years of therapy and are frequently found to have novel mutations in KIT or PDGFRA (that were not present in the primary tumor). These findings suggest the resistance to TKI therapy in these rare tumors is driven more by alternative mechanisms than through secondary Kit/PDGFRA mutations. Further study is needed to clarify these mechanisms as well as determine optimal treatment strategies.

5. Conclusions

In summary, we report a genetically unique case of rhabdomyosarcomatous dedifferentiation in a GIST following TKI therapy. Our case supports prior reports that these tumors behave in an aggressive fashion with early recurrence and resistance to TKI treatment. The molecular findings suggest that the resistance to TKI therapy in these rare tumors is driven more by alternative mechanisms than through secondary Kit/PDGFRA mutations. Further study is needed to clarify these mechanisms as well as determine optimal treatment strategies.

Conflict of Interests

The authors declare that they have no conflict of interests.

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