Case Reports

Could imatinib replace surgery in esophageal gastrointestinal stromal tumor

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are cellular spindle, or epithelioid tumors that occur in the stomach, intestine, and rarely in the esophagus. A 61-year-old man was complaining of resistant dry cough with dysphagia for one month duration. Upper gastrointestinal tract endoscopic examination showed a polypoid mass 30 cm from the incisors obstructing 50% of the lumen, where multiple biopsies were taken. Magnetic resonance imaging (MRI) showed a mass in the wall of the esophagus extending into the thoracic cavity. Histologically, the stained sections with the routine hematoxylin and eosin as well as the immunohistochemical stains for CD117, CD34, S100, vimentin, and smooth muscle actin confirmed the diagnosis of esophageal GIST. The patient was treated with imatinib, 400 mg/day. There was a dramatic reduction in the size of the tumor with successful improvement of his symptoms after 2 months of treatment, which was confirmed by repeated upper GIT endoscopy, and MRI.

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Primary mesenchymal tumors arising in the wall of the gastrointestinal tract (GIT) are rare and heterogenous compared with epithelial neoplasms, and their differentiation and biological behavior are continuing topics of controversy. The term gastrointestinal stromal (GIST) has been used to refer to the main group of mesenchymal tumors of the GIT; these are cellular spindle, or epithelioid tumors that show rudimentary if any smooth muscle differentiation. A great majority of GISTs occur in the stomach and intestine, and rarely occur in the esophagus. The GISTs account for 25% of esophageal stromal tumors (and leiomyomas for 70%), and involve lower third or gastroesophageal junction, predominantly in males. They can be spindled or epithelioid and display the usual variety of patterns.

The results of recent molecular pathologic studies showed that most GISTs are immunoreactive for CD34, a marker for dendritic fibroblastic interstitial cells, and CD117, a c-kit proto-oncogene protein, as well as the gain-of-function c-kit mutations that cause pathologic activation of the tyrosine kinase of c-kit in many GISTs, seem to support the concept of GISTs as a biologically distinct entity. In its wild type state, kit is a cell surface receptor whose natural ligand is stem cell growth factor. Due to the immunohistochemical and ultrastructural similarities between Cajal cells and GISTs; the histogenetic origin of GISTs from Cajal cells has been proposed. Most mutations in GISTs consist of in-frame deletions and single nucleotide substitutions within exon 11, which encodes the juxtamembranous domain; however, alterations have also been described in exons 9 and
13, which encode portions of the extracellular and kinase domains respectively. Mutant isoforms of c-kit become autonomous, they phosphorylate tyrosine residue on all types of signaling proteins that bind to or interact with them in the absence of the growth factor. Mutant kit receptors also phosphorylate each other called autophosphorylation. Under optimal conditions, approximately 95% of GISTs stain positive for CD117, and approximately 85% have c-kit mutation.

Imatinib mesylate is a signal-transduction inhibitor designed to selectively inhibit certain classes of tyrosine kinase that include the c-kit receptor expressed in GIST. Imatinib binds to activated c-kit receptors, and blocks the cell signaling pathway to prevent uncontrolled cell proliferation. In this study, we report a case of esophageal GIST showing dramatic regression of its size after imatinib mesylate treatment.

Case Report. A 61-year-old man was presented to outpatient clinic with the resistant dry cough and dysphagia for one month duration. He was an occasional smoker and a known hypertensive, and his blood pressure was well controlled with medication. He was admitted to the hospital for upper GI endoscopy. On endoscopy, there was a polypoid mass at 30 cm from incisors. The lesion was occupying 50% of the lumen of the esophagus. The mucosa was intact; multiple biopsies were taken. He had also undergone the magnetic resonance image (MRI), which revealed a big homogenous tumoral mass visible in the posterior mediastinum, and extending to the right hemithorax, measuring approximately 52 x 77 mm in the transverse axis (Figure 1). Histologically, the tumor was consisted of interlacing sheets of plump spindle cells with hyperchromatic nuclei separated by abundant delicate capillaries. The mitotic rate was 3/50 high power fields (HPF). The tumor cells were phenotype immunohistochemically by the streptavidin-biotin method using antibodies (DAKO) all diluted to 1:50 (Table 1). They were uniformly CD117 (Figure 2), CD34 and vimentin positive, while the immunoreactivity to smooth muscle actin (SMA) and S100 were negative. The MIB-1 immunostaining was nuclear and seen in 2% of tumor cells. Then the diagnosis of GIST was established, and he was treated with imatinib 400 mg/day. After 2 months of treatment, he was re-admitted to the hospital for re-assessment. There was a clear improvement in his symptoms. Upper GI endoscopy showed a polypoid tumor 30 cm from the incisors. The MRI revealed reduction in the size of the mass to 35 x 40 mm in transverse axis with obvious central cavitation within the mass (data not shown). He was discharged from the hospital and put on imatinib mesylate 400 mg/day.

Discussion. The use of CD117 immunostaining is highly essential to facilitate the diagnosis of GIST for spindle cell or epithelioid tumors arising in the GIT of middle aged or older persons. The CD117 is expressed not only in a variety of normal tissues (Cajal cells, mast cells), acute myeloid leukemia, mast cell disease, malignant melanoma, Ewing’s sarcoma, Hodgkin’s disease, anaplastic large cell lymphoma, germinomas, and gliomas, but also in spindle cell sarcomas of soft tissue, including leiomyosarcomas, dermatofibrosarcoma protuberans, hemangiopericytoma, malignant fibrous histiocytomas, synovial sarcomas, rhabdomyosarcoma, and fibrosarcomas. Thus immunostaining for CD117, which is not entirely specific but is a sensitive marker for GISTs, is mandatory for making a diagnosis, combined with careful morphologic examination and clinical correlation.

In this study, all the tumor cells showed diffuse positivity for CD117 and CD34, and on the contrary they showed no immunostaining for S100 and SMA as noted by others. Smooth muscle actin positivity showed a reciprocal relationship with CD34 expression; SMA-positive tumors were often CD34 negative. Under optimal conditions, approximately 95% of GISTs stain positive for CD117. Approximately 85% of GISTs have c-kit mutations, in some cases c-kit appears to be activated by a mechanism other than mutation. It has shown that many CD117-negative GISTs (4-5% of all GISTs) have mutations in another derived growth factor receptor alpha (PDGFRα). Tumors expressing c-kit or PDGFRα oncoproteins were indistinguishable with respect to activation of downstream signaling intermediates and cytogenetic changes associated with tumor progression. Importantly, some PDGFRα-positive GISTs respond to imatinib. A small but clinically relevant fraction of GI tumors will not be stained by antibodies to c-kit, but are still GISTs, and these patients deserve a trial of imatinib. While most anatomic pathologists use tumor size and mitotic count to estimate the likelihood that a GIST is malignant, Trupiano et al., a GI pathologist, believes this quantitative approach is basically flawed. He believes that neither mitotic counts nor gross measurements are reproducible. He evaluated 77 gastric stromal tumors looking for morphological features that define benign GISTs. He has found over the years that the most difficult thing to figure out is
what is benign, rather than defining malignant. The characteristics of benign epithelioid GISTs include a rounded or polygonal shape, abundant cytoplasm, which often looks peripherally clear, and cells with large or multiple nuclei. Benign spindle cells tend to be annoyingly uniform, and are arranged in long sweeping palisades. They tend to have small vacuoles indenting the nucleus at one edge.

The sensitivity was 100%, and specificity was 92%. He acknowledges that they are hard to diagnose and to determine whether they are benign or malignant unless we have experience with them. A recent study has shown that the outcome was strongly dependent on tumor size and mitotic activity. In general, tumors with 5 or fewer mitoses per 50 HP fields and those that are 5 cm or less in diameter are clinically favorable. The size of the tumor in our case is more than 5 cm in diameter, but the mitotic rate was less than 5/50 HPFs, and the MIB-1 index was 2%, we expect benign behavior for this tumor, especially when we take in consideration the good response to imatinib. Accurately qualifying GIST patients for imatinib therapy demands an antibody that provides strong consistent staining for c-kit and that has good specificity noted that virtually all GI specimens contain internal positive and negative controls. We have to make sure that normal structures; the mast cells that are almost always present are staining strongly and cleanly and that smooth muscle cells in tissue are not stained, also crush, and edge artifacts are possible, “cautions,” especially within small GI biopsies. It can also be helpful to recognize different staining patterns within the 2 GIST differentiation lines; the more common spindle cells and epithelioid cells. Spindle-cell GISTs stain more intensely with typically strong cytoplasmic staining with accentuation along the membrane. In another pattern, instead of diffuse cytoplasmic, and membrane staining, a perinuclear Golgi-like pattern predominates, and this pattern tends to be seen more often in epithelioid cells. Therefore, when we look at low power, epithelioid predominant-type GISTs might not appear to be stained as strongly and uniformly as you would expect.

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how long, the pH of the water, and many other steps. Having commercial patented antibodies does not get us over those hazards. Antibody standardization is going to be difficult, since we can’t control how people in different laboratories process specimens, one way forward is by providing similar known positive controls to which we can calibrate our local staining. Immunohistochemical accuracy will become even more important as it is increasingly used to detect biologically significant oncoproteins that have direct therapeutic applications. Application of antigen retrieval should be discouraged as it induces dramatic loss of specificity, and in any case it has to be stressed that CD117 immunopositivity “per se” does not predict at all sensitivity to imatinib.

In our case, there was a dramatic response of the tumor to imatinib mesylate 400 mg/day with nearly 40% shrinkage in the size of the tumor within 2 months period suggesting that imatinib mesylate can be used as a first line of treatment of GIST, and may overcome the need for surgery. The post treatment cavitation of the mass is due to the death of tumor cells secondary to the imatinib action on mutated kit receptors. Imatinib mesylate inhibits the mutated kit receptor observed in most GISTs, leading to the onset of apoptosis and decreased proliferation of tumor cells. Preliminary results of several trials indicate that imatinib mesylate is an effective, and safe treatment in patients with unresectable, recurrent, and metastatic tumors.

In conclusion, esophageal GIST can be diagnosed successfully by endoscopic biopsy with immunohistochemical staining for CD117 and CD34, and the use of imatinib is highly recommended in its treatment, which may substitute the need for surgery.

References