Malignant gastrointestinal stromal tumor of the tongue: case report and review of the literature

Hussein Hassan Hamed Ibrahim, BDS, HDD, MDS, PhD,a Mahmoud Sayed Ahmad, MBCh, DTM&H, MSc, MD,b Wadah Abdo Eskaf, MSc,c and Petr Schütz, MD,d Kuwait

AL-ADAN DENTAL CENTER, AL-AHMADI GOVERNORATE, AL-FARWANIYA HOSPITAL, AL FARWANIYA GOVERNORATE, AND KUWAIT CANCER CONTROL CENTER, AL-ASIMAH GOVERNORATE

A case of malignant gastrointestinal stromal tumor (GIST) of the tongue is reported. The patient was a 60-year-old woman. She underwent extended hemiglossectomy, neck dissection and reconstruction of the defect with radial forearm microvascular free flap. Etiology, histopathology, differential diagnosis, clinical presentation, and treatment of GISTS are discussed. The absence of any previous report in the English-language literature about the occurrence of GIST in the tongue is emphasized. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e24-e29)

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract with the exception of the esophagus. In earlier literature, GISTs were classified as smooth muscle tumors: leiomyomas, leiomyoblastomas, and leiomyosarcomas. The first doubts about their histogenesis were based on electron microscopic studies, which revealed lack of typical smooth muscle differentiation. The investigators noted that although some cells in these tumors appeared to be capable of partial or imperfect smooth muscle differentiation, the basic cells were poorly differentiated. Well developed features of smooth muscle differentiation were difficult to find. This suggests that the tumor cells represent varying morphologic expressions of primitive mesenchymal precursor cell with smooth muscle potential. It has been suggested that GISTs originate from the interstitial cells of Cajal (ICC), or from a primitive stem cells that differentiate toward both the ICC and smooth muscle phenotype. ICC are unique pacemaker cells that are interposed between the autonomic nervous system and the muscular wall of the bowel and are responsible for coordinating peristalsis. Although GISTs were originally described in the stomach and small intestine, some cases have been subsequently reported in the rectum, esophagus, omentum, mesentery, and other extragastric sites. To our knowledge we present the first case of GIST involving the tongue.

CASE PRESENTATION

A 60-year-old female patient attended our unit with the chief complain of an ulcer on the right lateral margin of the tongue of ~6 weeks' duration. Apart from noninsulin-dependent diabetes mellitus of 5 years' duration, she had no significant medical history. The clinical examination revealed ulcerated mass of the right side of the tongue about 2 × 2 cm in diameter (Fig. 1). The ulcer had a necrotic floor with inflamed margin, and the mass was hard in consistency and pink to white in color. The lesion was painless, and the regional lymphatic nodes were not palpable. Incisional biopsy were done, and the result of the histopathologic examination was stromal sarcoma of the tongue of low-grade malignancy. The patient was admitted to the hospital, where she underwent tracheostomy, suprahyoid neck dissection, extended hemiglossectomy via mandibulotomy, and reconstruction of the defect with radial forearm microvascular free flap. The postoperative course was uneventful, and operation wounds healed primarily; however, the patient suddenly died from unknown reason about 3 weeks after discharge from the hospital.

Histopathologic Findings

Right hemiglossectomy specimen 4 × 3 × 3 cm in size contained 3 × 2.5 × 2-cm tumor mass with ill-defined margins and 2.5 × 2 cm mucosal ulcer. Sections from the tongue showed a mixed inflammatory
cell infiltrate at the site of the ulcer, beneath which there was a tumor proliferation composed of short interlacing strands and fascicles of spindle cells, running in different directions. These tumor cell formations infiltrated the underlying stromal tissue and the tongue skeletal muscles (Fig. 2). The tumor cells had elongated, blunt-ended, cigar-shaped, focally hyperchromatic nuclei and acidophilic cytoplasm (Fig. 3). Mild to moderate pleomorphism and frequent mitotic figures, few of them abnormal, were seen (Fig. 4). There were areas of myxoid change and scattered lymphocytic infiltrate. No evidence of tumor necrosis or vascular permeation was seen. At this stage, the diagnosis of malignant spindle cell tumor was decided by the pathologist. Immunohistochemical study to reach the final diagnosis was then carried out, and stains for cytokeratin, smooth-muscle actin, S100, myosin, and vimentin was done. The result was not specific: focally positive for smooth-muscle actin and vimentin and negative for S100, myosin, and cytokeratin. So staining of CD117 was done, which was diffusely positive in the tumor (Fig. 5). The final histopathologic diagnosis based on the above findings was malignant GIST of the tongue.

**DISCUSSION**

Microscopically, the 2 basic types of cells found in GIST are the spindle-cell type and the epithelioid or round-cell type. Some tumors may have an admixture of both cells. Spindle-cell type is the predominant pattern, seen in 70% of GIST cases. A spindle-cell GIST consists of cigar-shaped cells with elongated nuclei with tapered, blunt, or rounded ends frequently with a clear perinuclear halo and moderately abundant pink
cytoplasm. These cells may be arranged in bundles of interlacing fascicles resembling smooth muscle tumors, or they may have a palisading pattern resembling nerve sheath tumors or a vague compartmental pattern. GISTs with epithelioid morphology account for \( \frac{1}{5} \) of cases. The epithelioid GISTs contain polygonal or round-shape cells. The tumor cells exhibit eosinophilic or clear cytoplasm. The cytoplasm may be retracted, simulating cytoplasmic inclusions. The nuclei tend to be round to ovoid and may be pushed to an eccentric location. The tumor cells are arranged in sheets or may have a nested organoid growth pattern.

GISTs of mixed cell type may feature an abrupt transition between spindle-cell and epithelioid areas or may show an intermediate ovoid cytologic appearance. A small minority of GISTs (\(<5\%\)) have extensive nuclear pleomorphism. The stroma exhibit eosinophilic or clear cytoplasm. The cytoplasm may be retracted, simulating cytoplasmic inclusions. The nuclei tend to be round to ovoid and may be pushed to an eccentric location. The tumor cells are arranged in sheets or may have a nested organoid growth pattern.

In the pathogenesis of GISTs, the major role belongs to c-KIT mutations. It was found that the best defining feature of the GISTs is the expression of c-KIT protein (also known as CD117).\(^{10,18-20}\) c-KIT protein is a type III receptor of tyrosine kinase that is involved in the development and maintenance of germ cells, mast cells, erythrocytes, melanocytes, and ICC. c-KIT is a transmembrane protein with an extracellular ligand-binding domain and an intracellular kinase domain. The ligand for c-KIT is known as stem cell factor. Binding of the stem cell factor results in c-KIT dimerization/oligomerization and autophosphorylation/activation through the phosphorylation of critical tyrosine residues.

Subsequent to autophosphorylation/activation, c-KIT phosphorylates other signal-transduction proteins. Many of them also have kinase activity, resulting in modulation of cellular behaviors, including cellular proliferation, chemotaxis, and apoptosis.\(^{21}\) The c-KIT positivity of GISTs is strong and nearly uniform. Other tumors that may be also c-KIT positive (melanoma, angiosarcoma, pulmonary small cell carcinoma, Ewing sarcoma, mastocytoma, and seminoma) are only rarely considered in differential diagnosis of GISTs.\(^{7}\) Approximately 5% of GISTs have intragenic activation mutations in platelet-derived growth factor receptor-alpha (PDGFRA). PDGFRA is a member of the same family of receptor tyrosine kinases as KIT, and therefore is structurally very similar. Mutations of c-KIT and PDGFRA seem to be mutually exclusive oncogenic events in GISTs.\(^{21}\) There are some other immunohistochemical markers important in diagnosis of GISTs. Approximately 60%-70% of tumors are positive for CD34, the hematopoietic progenitor cell antigen. A significant number (20%-30%) of GISTs express smooth-muscle actin, typically present in smooth muscle cells and myofibroblasts. GISTs are rarely positive for S100 protein (10%), and desmin, an intermediate filament protein typical for smooth, skeletal, and cardiac muscle cells, has been found in only 2%-4%.\(^{13,16}\) The immunohistochemical staining for the present case was positive for CD117, focally positive for smooth-muscle actin, and vimentin, and negative for S100, myosin, and cytokeratin.

Recently, protein kinase C theta (PKC\(\theta\)) was identified in gene expression profiling studies to be specifically and strongly expressed in GISTs. PKC\(\theta\) is a signaling molecule known to play a role in activation of the T-cells, neuronal differentiation and skeletal muscle signal transduction. The preliminary studies have shown that PKC\(\theta\) is strongly expressed in GISTs and is sensitive and specific for the diagnosis of GISTs by immunohistochemical studies.\(^{22-24}\)

GISTs have a wide spectrum of clinical presentation and behavior, from incidentally detected nodules to bulky tumors. The benign GISTs are usually sharply demarcated spherical or ovoid fusiform nodules 2-5 cm in diameter bulging outward or inward, sometimes with mucosal ulceration. However, the malignant GISTs are usually larger and often show mucosal ulceration and areas of necrosis and hemorrhage similar to the clinical picture of the present case.\(^{2,16}\) It was reported that GISTs do not disseminate to the regional lymph nodes.\(^{15,16}\) However, other studies recorded rare events of lymph node metastases.\(^{25}\) In the present case, there was no lymphadenopathy. Distant metastasis most commonly occurs to the liver and

![Fig. 5. Immunohistochemical stain showing the tumor cells positive for CD117 (CD117, ×400).](image-url)
rarely to the lung and bone.\textsuperscript{2,15} In the present case we did not discover any distant metastasis.

The patient in this case was female; some studies show no significant gender predominance,\textsuperscript{16} and others show a male predominance.\textsuperscript{25} Older adults are at risk for GIST, with peak incidence between 40 and 80 years of age at the time of diagnosis, with a median age of \(~60\) years, which was similar to the present patient.\textsuperscript{14,16} Very rarely, GISTs occur in children and young adults, sometimes connected with Carney triad\textsuperscript{13,14,26} or on a familial basis.\textsuperscript{27,28}

GISTs have been documented in all parts of the gastrointestinal tract (GIT). A great majority of them occur in the stomach (60\%-70\%) and small intestine (25\%-35\%), with rare occurrence in the colon and rectum (5\%), esophagus (<5\%), and appendix. Rarely, GISTs are found outside the gastrointestinal tract and are collectively known as extragastrointestinal stromal tumors (EGISTs), e.g., uterus, rectovaginal septum, vagina, mesentery, omentum, or retroperitoneum.\textsuperscript{2,13-15}

The prognosis and risk of GISTs have been the subject of study by many authors. The prognostic significance of the c-KIT mutation is controversial. It was reported in an earlier study that c-KIT mutations occur preferentially in malignant version of GISTs; however, it was found that presence or absence of mutation itself does not separate GISTs into benign or malignant.\textsuperscript{15,21}

Other prognostic features that have been evaluated are the Ki-67 proliferative index and the telomerase activity. The increase in Ki-67 proliferative index have been evaluated as an indication for poor prognosis, but other studies have failed to support this finding. Also, some studies identified telomerase activity in clinically aggressive lesions, but with no series large enough to support this.\textsuperscript{14,21} The cellular and mucosal invasion have also been evaluated for their prognostic significance. Low cellularity has emerged as a favorable factor for defining the risk of aggressive behavior rather than classifying the lesion as either benign or malignant. These guidelines were developed during a consensus conference at the United States National Institutes of Health in April 2001.\textsuperscript{21}

Some authors stress on the importance of the tumor site in predicting prognosis. The extragastric tumors are more likely to behave in a more aggressive fashion than gastric ones, independent of the tumor size and mitotic count, with the small bowel tumors having the worst prognosis. This provided a rationale for the proposed site-specific evaluation of GISTs\textsuperscript{2,14,15,30-32}; however a recent study on 1,765 GISTs does not support this concept.\textsuperscript{33} Another study found that invasion of the adjacent organ at the time of surgery was associated with a highly aggressive behavior.\textsuperscript{25,31}

Surgery is the main modality of therapy, but even after adequate resection the vast majority of GISTs recur, and in \(~50\%\) the liver is the main site of the metastasis. In the view of high postoperative recurrence, adjuvant forms of therapy are being explored, and the tyrosine kinase inhibitor imatinib mesylate, formerly known as STI-571, holds the greatest promise. In cases such as metastatic or inoperable tumors, imatinib mesylate, which acts specifically on the growth factor receptor of this tumor, has been used with documented improvement. Imatinib mesylate has been shown to decrease the density of tumor cells without causing inflammation or necrosis\textsuperscript{34,35}; however, it has become clear that some patients do not respond to it and others develop resistance. The role of imatinib in the adjuvant and neoadjuvant setting of primary GISTs is therefore not yet certain. Recently, there has been a considerable effort for the development of other anti-GIST therapies, such as SU11248.\textsuperscript{21}

Consensus points in clinical management of GIST as well as questions for future clinical trials were identified during the consensus conference on GIST management. Thirty-two consensus points were identified. Among these, the standard histologic examination with immunohistochemical analysis using CD117, CD34, S100, desmin, and smooth-muscle actin is considered to be standard. Complete tumor resection with negative tumor margins is the standard surgical treatment. Adjuvant and neoadjuvant forms of therapy are being explored, and the tyrosine kinase inhibitor imatinib mesylate, formerly known as STI-571, holds the greatest promise. In cases such as metastatic or inoperable tumors, imatinib mesylate, which acts specifically on the growth factor receptor of this tumor, has been used with documented improvement. Imatinib mesylate has been shown to decrease the density of tumor cells without causing inflammation or necrosis\textsuperscript{34,35}; however, it has become clear that some patients do not respond to it and others develop resistance. The role of imatinib in the adjuvant and neoadjuvant setting of primary GISTs is therefore not yet certain. Recently, there has been a considerable effort for the development of other anti-GIST therapies, such as SU11248.\textsuperscript{21}

Soft tissue sarcomas comprise a group of relatively rare, but anatomically and histologically diverse, neoplasms. Soft tissue sarcomas of the head and neck account only for \(<5\%\) of all sarcomas, and the oral
sarcomas are even rarer. The majority of the literature consists of single case reports and a few case series. The present case report adds one more site, the tongue, to the malignant stromal tumors of the gastrointestinal tract known as GISTs. To the best of our knowledge, no case of GIST of the tongue has been reported in the English-language medical literature. This may be partly due to the difficulty in differentiating smooth muscle tumors from GISTs on histology alone.

In this case we performed surgical excision and reconstruction, in agreement with many authors who have reported that complete surgery without rupture remains the mainstay of treatment in patients with localized resectable GISTs. In terms of age, incidence, gross morphology, and histopathology, this case resembled the commonly found GIST. However, we believe that the cause of death in this patient was presumably not related to this tumor.

The authors acknowledge the histopathologist involved in the diagnosis of this case, Dr. I. Francis. They also thank Prof. S. Šafár, Dr. M. S. Belal, Dr. N. Al-Zohery, Dr. N. Rajacic, and Dr. J. Abd Al-Kader, who were the other surgeons involved in this case.

REFERENCES

33. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical,

Reprint requests:
Dr. Hussein Hassan Hamed Ibrahim
PO Box 51691
Al Riqqa 53457
Kuwait
hussein20022002@hotmail.com