A 58-year-old man with a past medical history of hepatitis C and hypertension was referred to Baylor University Medical Center to evaluate occult gastrointestinal bleeding with double-balloon endoscopy. Before coming to Baylor, he complained of fatigue, shortness of breath, and noted melena. Upper endoscopy and colonoscopy were unrevealing. Capsule endoscopy at the outside hospital suggested a proximal bleed in the small bowel. Imaging included an ultrasound that showed a 6-mm common bile duct with cholelithiasis and an angiogram with findings of a proximal jejunal blush suggestive of the site of bleeding. At the outside hospital, he had an initial hematocrit of 23% and received 3 units of packed red blood cells. While his hematocrit rose with the transfusion, it further declined during treatment with a proton pump inhibitor, and he remained symptomatic.

The patient’s past medical history included a right carotid artery aneurysm resulting in a cerebrovascular accident that limited the use of his right arm, as well as a hiatal hernia, benign prostatic hypertrophy, chronic lower back pain, arthritis, Horner’s syndrome, and a right knee surgery. His medications included ondansetron, pantoprazole, lisinopril, tramadol, docusate, and diphenhydramine. The family history was positive for strokes and diabetes.

On physical examination, he was noted to have multiple cherry angiomas on his right arm, as well as a 5-cm hyperpigmented café-au-lait macule on his right neck, axillary freckling, and palpable, nontender nodules on his abdomen and extremities. Suspecting neurofibromatosis 1 (NF1), multiple Baylor physicians inquired about a history of this disease, and he denied any previous diagnosis or family history.

**ENDOSCOPIC FINDINGS**

Double-balloon endoscopy revealed multiple arteriovenous malformations in his small bowel that were cauterized and two submucosal nodules in the jejunum suggestive of a gastrointestinal stromal tumor (GIST) (Figure 1).

**RADIOLOGICAL FINDINGS**

The patient was referred to the radiology department for evaluation of the chest, abdomen, and pelvis with computed tomography (CT) for the masses in the jejunum discovered during endoscopy. He underwent examination with routine 5-mm transaxial images through the chest, abdomen, and pelvis following the intravenous administration of 100 cc of Omnipaque 350 and 500 cc of oral Gastrografin. The abdomen demonstrated two regions of abnormal small bowel: the first was located within the proximal jejunum and was seen as an ill-defined, somewhat exophytic lesion extending from the mesenteric wall (Figures 2a and 2b), and the second involved the jejunum slightly distal to...
this first lesion and displayed concentric jejunal wall thickening (Figure 2c). At the time of initial interpretation, it was thought that this second lesion could represent focal bowel peristalsis; however, when correlated with endoscopic findings, it was believed to be one of the many known small bowel lesions. The remainder of the intra-abdominal and intrapelvic contents was normal. A subcutaneous nodule was incidentally noted within the right paraumbilical tissues (Figure 3).

Imaging of the chest was largely unremarkable with the exception of incidentally noted expansion of the spinal canal and right neural foramen at the cervicothoracic junction. The vertebral bodies at this level were hypoplastic. This region of the body was incompletely visualized with this examination, and the patient was referred for magnetic resonance imaging (MRI) of the cervical spine for evaluation of these findings.

MRI revealed extensive abnormalities, including gross misalignment of both the upper and lower cervical spine (Figures 4 and 5). The C4, C5, C6, and C7 vertebral bodies were markedly hypoplastic with posterior scalloping present, suggesting dural ectasia. Severe hypoplasia of the posterior elements of these vertebrae was present as well. No mass lesion or abnormal enhancement was noted on post-gadolinium imaging.

**SURGICAL FINDINGS**

The area of tumor appeared to be the site of bleeding in this patient, and he was referred for surgical resection of the affected segment of intestine.

The patient was explored laparoscopically, which has previously been reported as efficacious in patients with multiple NF1-associated GISTs (1). The mass of interest was easily identified in the proximal jejunum. It was a 2- to 3-cm exophytic mass originating from the antimesenteric border of the jejunum. In addition, multiple small, red nodules were identified along the jejunum and proximal ileum, away from the visible tumor, measuring 2 to 3 mm in size. Given the number and distribution of the suspicious nodules, it was not possible to remove all of them. The patient’s bleeding resolved after the surgery, and he had an uneventful postoperative course. He returned home after a short hospital stay.

**PATHOLOGICAL FINDINGS**

Several specimens were sent for pathologic evaluation. The main lesion in the proximal jejunum showed multiple subserosal and intramural spindle cell nodules consistent with multifocal GIST (Figure 6). The largest lesion was 2.2 cm. An additional biopsy specimen from the small bowel, as well as a serosal nodule in the distal jejunum, showed a microscopic area of interstitial cell of Cajal (ICC) hyperplasia, an early GIST tumor. In addition, an abdominal subcutaneous nodule was shown to be a neurofibroma (Figure 7), and a liver biopsy demonstrated chronic inflammation suggestive of chronic hepatitis, as well as focal mild portal fibrosis.

Immunohistochemical tests of the main specimen were negative for smooth muscle actin and desmin and positive for CD34 and CD117. Positive CD34 and CD117 in conjunction with the histomorphology of the lesions support the diagnosis of GIST. The proliferative marker MIB-1/Ki-67 stained 5% of the tumor cells. Further, the abdominal subcutaneous nodule was S100 positive. The S100 immunostain, among other things, stains neural tissue. In light of the morphologic findings and the concomitant GIST, this supports the diagnosis of the abdominal nodule as neurofibroma.

![Figure 3. Axial contrast-enhanced CT image of the abdomen showing a nonspecific subcutaneous nodule in the right paraumbilical soft tissues.](image1)

![Figure 4. An incidental finding on contrast-enhanced axial CT of the cervicothoracic junction: an abnormal C7 vertebral body with dural ectasia and expansion of the right neural foramen.](image2)

![Figure 5. T2-weighted sagittal MRI of the cervical spine showing (a) marked dural ectasia with posterior vertebral body scalloping and (b) hypoplastic vertebral bodies and malalignment.](image3)

![Figure 6. The gastrointestinal stromal tumor. (a) The main lesion in the proximal jejunum (10x) showing normal small bowel mucosa on the left and the lesion in the submucosa on the right. (b) A higher-power view of the lesion, which is characterized by palisading spindle cells.](image4)
NF1, also known as von Recklinghausen disease, is an autosomal dominantly inherited disease. Various abnormalities can be seen in this disease, with lesions arising from neuroectodermal and mesenchymal embryologic origins. The NF1 gene has been identified on chromosome 17q11.2. It encodes neurofibromin, a protein that is a member of the GTPase protein family of RAS regulatory proteins.

According to the National Institutes of Health guidelines, NF1 is a clinical diagnosis necessitating two of the following criteria: 1) six or more café-au-lait macules >5 mm in diameter; 2) two or more neurofibromas; 3) freckling in the axillary or inguinal regions; 4) optic glioma; 5) two or more Lisch nodules (iris hamartomas); 6) sphe- noid dysplasia or thinning of long bone cortex; and/or 7) a first-degree relative with NF1 (2–4).

While the diagnosis of NF1 remains clinical, it is associated with a wide range of anatomic and radiographic abnormalities. The central nervous system commonly displays optic nerve gliomas as well as white-matter hamartomas with the occasional low-grade brainstem gliomas. Spinal manifestations include dural ectasia, which leads to posterior vertebral body scalloping, neural foramen expansion, and lateral meningoceles. The structural spinal abnormalities lead to varying degrees of abnormal alignment, including scoliosis and abnormal kyphosis/lordosis, as seen in our patient (5, 6). Classic plain film findings that suggest NF1 are hypoplasia of the sphenoid wing, anterior bowing of the tibia and fibula, and ribbon ribs. Many different abdominal tumors can be present including GISTs (as seen in our patient), various adenocarcinomas and sarcomas, neurogenic tumors, carcinoid tumors, and pheochromocytomas (7).

GIST and NF1

GISTs are one of the most frequent nonepithelial tumors of the gastrointestinal tract. They are thought to develop from the ICC. GISTs and ICC express CD34 and type II receptor tyrosine kinase KIT.

The prevalence of GIST is 4% to 25% in those with NF1 (8, 9), compared with about 0.0015% (1.5 per 100,000) in the general population (10). Thus, those with NF1 are 25 to 250 times more likely to develop GISTS than those without NF1. There are numerous differences between sporadic GISTs and NF1-associated GISTs. For example, GISTS in NF1 patients are usually multiple instead of single, are larger in size, and are more likely to be found in the small intestine (Table) (11).

Patients with NF1 and GIST may be asymptomatic or may present with symptoms such as abdominal pain, abdominal mass, nausea, vomiting, dyspepsia, anemia, melena, hemateme- sis, hematochezia, intussusception, volvulus, small bowel obstruction, and fever; these presenting symptoms are no different in sporadic and NF1-associated GISTs (12). In one study of 45 patients with NF1 and GISTs, 63% presented with gastrointestinal bleeding, similar to our patient (13). That study showed that most patients with long-term follow-up had a good prognosis. After a median follow-up of 13.6 years, 20 of their 45 patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Sporadic GISTs</th>
<th>NF1-associated GISTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>10–20/million per year in the general population</td>
<td>Unknown</td>
</tr>
<tr>
<td>Mean age at presentation</td>
<td>60 years</td>
<td>50 years</td>
</tr>
<tr>
<td>Seen at younger ages?</td>
<td>Rare &lt;40 years (except in familial GIST)</td>
<td>Common &lt;40 years</td>
</tr>
<tr>
<td>Sex</td>
<td>M = F</td>
<td>M = F</td>
</tr>
<tr>
<td>Multiple or synchronous tumors</td>
<td>Uncommon</td>
<td>Very common</td>
</tr>
<tr>
<td>Anatomical site</td>
<td>50%–60% gastric; 25%–30% small intestine; 10% colon/rectum; 5% esophagus</td>
<td>40%–60% jejunal; 25%–75% other small intestine; 2%–25% gastric</td>
</tr>
<tr>
<td>Anatomical site prognosis</td>
<td>Gastric may be more favorable; small intestine, rectum may be less favorable</td>
<td>Jejunum more favorable; duodenum less favorable</td>
</tr>
<tr>
<td>Presence of ICC hyperplasia</td>
<td>Rare in sporadic GIST; common in familial GIST</td>
<td>Common</td>
</tr>
<tr>
<td>Size of tumor at presentation (all sites)</td>
<td>Smaller</td>
<td>Larger</td>
</tr>
<tr>
<td>Risk profile at diagnosis</td>
<td>30% overtly malignant</td>
<td>Usually low risk; often indolent course</td>
</tr>
<tr>
<td>Morphology</td>
<td>70% spindle; 20% epithelioid; 10% mixed</td>
<td>Typically spindle; minority with epithelioid features</td>
</tr>
<tr>
<td>KIT/PDGFRA mutations</td>
<td>85%–90% with KIT or PDGFRA mutations; NF1, neurofibromatosis 1</td>
<td>Uncommon; reported KIT and PDGFRA mutations are atypical</td>
</tr>
</tbody>
</table>

GIST indicates gastrointestinal stromal tumor; ICC, interstitial cell of Cajal.
*Reprinted with permission from Stewart et al, 2007 (11).

Table. Summary of features in sporadic and NF1-associated gastrointestinal stromal tumors*
were alive and well. Seventeen were alive with no evidence of disease versus five who were dead of the disease (13).

The molecular pathogenesis of NF1-associated GISTs may differ from that of sporadic GISTs. Although NF1-associated GISTs express c-kit, few have the typical activating mutations in exon 9 or exon 11 seen in sporadic GISTs (13–15). Mutations in proto-oncogene c-kit translate into constitutive activation of the KIT kinase and gain of function considered to be the primary oncogenic pathway in GISTs. Some researchers have suggested that NF1 mutations inactivate KIT-inhibitory phosphatases and thus cause overexpression of KIT or PDGFRα, which could be significant in GIST development (14). This is supported by recent demonstrations that KIT activation is ubiquitous in GISTs and that KIT tyrosine phosphorylation is prominent even in tumors without clear KIT mutations (16, 17).

Issues regarding c-kit mutations may have an impact on the treatment of patients with NF1-associated GISTs. In recent years, the treatment of patients with advanced or inoperable GISTs has been significantly advanced with the introduction of imatinib mesylate (IM), a small-molecule selective inhibitor of KIT and PDGFRα. This orally available drug has shown remarkable effect in most GISTs—tumors that were generally considered chemoresistant (18). Recently, it has been shown that certain c-kit mutations predict for higher response rates with IM; specifically, patients with exon 9 mutations appear to have higher response rates and improved survival compared with other patients with GISTs. NF1-associated GISTs typically lack these mutations and may not be responsive to IM. However, Lee and colleagues reported a favorable response to IM in a 65-year-old woman with NF1-associated GISTs who did not have mutations in the KIT or PDGFRα gene (19). Sunitinib, a drug similar to IM, has also shown clinical effectiveness in GISTs, and one case report has described the successful use of sunitinib in an NF1 patient with metastatic GIST (20).

Based on the limited information available on the effect of IM and sunitinib and the fact that GISTs in NF1 patients tend to have an indolent course, it was decided not to use these drugs as treatment for this patient at this time. Although the patient is no longer bleeding, known disease was left behind; further, the patient is susceptible to other tumor types, which needs to be considered and further evaluated. Continued monitoring, including positron emission scanning, capsule endoscopy, as well as KIT and PDGFRα mutation analysis, are planned for this gentleman with multiple GISTs and a clear clinical picture of NF1.