Multiple Gastrointestinal Stromal Tumors and Lipomatosis

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In this report, we describe a 36-year-old man with the synchronous occurrence of multiple gastric gastrointestinal stromal tumors and multiple intestinal lipomas. Multiple, small, and well-circumscribed gastric gastrointestinal stromal tumors (3 mm to 2 cm) were present within the gastrectomy specimen. The gastrointestinal stromal tumors were composed of epithelioid cells that were strongly positive for CD117 but negative for S100 protein or smooth muscle–specific actin. Also, 17 small submucosal lipomas were identified in the duodenal portion of the gastrectomy specimen. Endoscopic follow-up of the patient revealed more than 20 additional lipomas scattered throughout the intestine. Several large intestinal lipomas were resected endoscopically and histologically confirmed. Although both multicentric gastrointestinal stromal tumor and gastrointestinal lipomatosis have been reported in association with a few genetic syndromes, there has been no report, to our knowledge, of their coexistence. We feel that the coexistence of multiple lesions of these 2 rare diseases in this relatively young patient may represent a novel syndrome.

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Gastrointestinal stromal tumor (GIST) is a relatively common primary nonepithelial tumor arising in various parts of the gastrointestinal tract. It usually presents as a sporadic, solitary tumor. Most GISTs have a relatively unique morphohistology. Conventional GISTs consist of a proliferation of spindle cells or epithelioid cells or both. Recent advances have greatly enhanced the diagnosis of this tumor by using immunohistochemical markers. More specifically, most GISTs have mutations of the c-kit gene, which lead to constitutive and excessive activation of the signaling pathway plays a significant role in the tumorigenesis of GISTs. As a result, the tyrosine kinase inhibitor imatinib mesylate (IST1571) now has a significant role, in addition to surgical resections, in the management of GIST. One third of the GISTs with wild-type c-kit have been found to have activating platelet–derived growth factor receptor α (PDGFRα) gene, and the c-kit and PDGFRα mutations appear to be mutually exclusive.

Multiple GISTs are relatively rare, and they are often associated with some genetic syndromes or in a familial form. For example, GISTs have been associated with neurofibromatosis type 1 (von Recklinghausen disease) or Carney triad syndrome. A familial syndrome of GISTS and paraganglioma has also been described. GISTS associated with neurofibromatosis type 1 (NF1) have unique clinical, phenotypic, and genotypic characteristics; these tumors are likely to be multicentric, to originate in the small bowel, and typically are composed of spindle cells.

Although most GISTs associated with NF1 are immunohistochemically immunoreactive for CD117, they usually do not have activating c-kit or PDGFRα mutations.

Although uncommon, lipomas in the gastrointestinal tract are well recognized at endoscopy. The prevalence of gastrointestinal lipoma is reported to range from 0.2% to 5.8% depending on the population of patients in the particular study. Histologic features of lipoma are relatively bland and are characterized by localized masses of mature adipose tissue with an overlying intact or eroded mucosa, and a thick fibrous capsule surrounds the tumor. Multiple lipomas (>4) and lipomatosis are very rare with a reported prevalence of approximately 0.2% in one large autopsy series. The number of lipomas required to diagnose lipomatosis is not clear. Amato et al described a case as lipomatosis that had 3 distinct lipomas in one segment of sigmoid colon. However, other authors use quite different criteria for the diagnosis. For example, Catania et al reported lipomatosis when more than 100 submucosal sessile and polypoid lipomas throughout the colon were identified and when, applying the same criteria, the authors found 12 additional cases of gastrointestinal lipomatosis in a review of the literature dating back to 1931.

Lipomatosis has been occasionally associated with hamartomatous syndromes. For example, in rare reports, the association of lipomatosis with NF1 is noted. Soft tissue lipomatosis has been reported to be associated with Proteus syndrome, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome, 3 conditions characterized by mutation of the phosphatase and tensin homolog (PTEN) gene. One case of lipomatosis associated with small in-
The coexistence of multiple lesions of these 2 diseases in the gastrointestinal tract in this relatively young patient prompted us to hypothesize that it may represent a potentially novel syndrome with unknown underlying genetic alterations.

**REPORT OF A CASE**

A 36-year-old white patient had a long history of intermittent epigastric and abdominal pain and retrosternal burning sensation and a recent development of gastric outlet obstruction symptoms (regurgitation and vomiting of food that he had eaten 2 to 3 days earlier). By endoscopy he was found to have gastric outlet obstruction and had a gastrectomy for relief of his obstruction at an outside hospital. By report, gross examination of the gastrectomy specimen revealed the presence of multiple small and wide-spaced nodules measuring from 3 mm to 2 cm in the muscularis propria of the stomach. The diagnosis of multiple GISTs was confirmed both histologically and immunohistochemically. As shown in Figure 1, A and B, the tumors were composed of nodular proliferations of epithelioid cells. In this patient, the epithelioid cells were the predominant population, and a significant number of inflammatory cells were scattered around the vessels throughout the tumors. Plump spindle cells with slightly prominent intercellular collagen bands were focally present in a few tumors (Figure 1, C). The tumors did not have necrosis, and mitotic activity was extremely low (1 mitotic figure per 50 high-power fields). When analyzed by immunohistochemistry, the tumor cells had a strong membranous and cytoplasmic CD117 expression (Figure 1, D), the protein encoded by the c-kit gene. Consistent with the literature, the tumor cells were not immunoreactive to anti-smooth muscle-specific actin (SMA) or S100 protein antibodies (Figure 1, E and F). Also, within the gastrectomy specimen, 17 small submucosal lipomas were identified in the duodenum.

The patient did well after surgery and came to our hospital for postsurgery follow-up and consultation because of the unusual findings in his gastrectomy. He was asymptomatic during the follow-up period of approximately 20 months. Review of the patient’s medical history was unremarkable, except for the multiple gastric GISTs and duodenal lipomas. Review of the patient’s family medical history was unremarkable. Physical examination showed no café au lait spots or neurofibromas. Esophagogastroduodenoscopy at our institution, 4 months after surgery, revealed the presence of several small sessile lipomas in the residual duodenum and jejunum. Colonoscopy 2 months later revealed the presence of more than 20 lipomas in the ileum, right colon, and left colon. The lipomas were more concentrated in the left colon. As shown in Figure 2, A, the endoscopic images of the polypoid lipomas had an “angry” appearance, with subepithelial hemorrhage and a purplish hue to the head of the polypoid lipomas.

The 3 large polypoid lipomas in the colon were removed endoscopically. These polypoid lipomas measured 1.7 to 2.4 cm in the maximal dimension grossly and had a typical appearance under colonoscopy, when these lesions were exposed by incision of the overlying mucosa (Figure 2, B). As shown in Figure 3, A and B, these tumors were mainly composed of mature adipose tissue with some fibrous tissue and vasculature confirming the diagnosis of lipoma. Compared with conventional lipomas, these lipomas had abundant fibrous tissue and prominent vascular pattern (image not shown). However, the amount of fibrous tissue and vessels was not adequate for a diagnosis of angiomylipoma and stains for HMB-45 were negative.

Because the cells from multiple GISTs in this patient were strongly immunoreactive for CD117, we hypothesized that the lipoma cells may also have immunoreactivity for CD117. Im-

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**Figure 1.** A and B, Gastrointestinal stromal tumors (GISTs) with proliferation of epithelioid cells with distinct cell border, vacuolar cytoplasm, and vesicular nuclei (hematoxylin-eosin, original magnifications ×50 [A] and ×400 [B]). C, Some GISTs show plump spindle cells with vesicular nuclei and slight, prominent intercellular collagen bands (hematoxylin-eosin, original magnification ×400). D, GIST cells show strong membranous and cytoplasmic staining for CD117, the protein product for the c-kit gene, as detected by immunohistochemistry (original magnification ×100). E, The tumor cells show no expression of smooth muscle–specific actin as detected by immunohistochemistry (original magnification ×100). F, The GIST cells show no expression of S100 protein as detected by immunohistochemistry (original magnification ×100).
Figure 2. The typical endoscopic appearance of one of the intestinal lipomas. A, The lipoma is a pedunculated lesion with an intact mucosa (the arrow marks the lipoma). B, A well-encapsulated lesion consists of greasy, yellow material (the arrow) in the lesion upon removal of the surface mucosa.

Figure 3. Histologic features of the intestinal lipoma. A, The lipoma is well demarcated and is located in the submucosal area. It consists of mature fat encapsulated by a fibrous capsule. B, Higher magnification showing mature adipose tissue (hematoxylin and eosin, original magnifications ×100 [A] and ×200 [B]).

COMMENT

GISTs constitute the majority of primary nonepithelial neoplasms of the stomach. The morphology and immunohistochemical features of this tumor have received increasing attention in recent years. The most important advance has been the discovery that most GISTs are accompanied by somatic mutations of the c-kit gene, a tyrosine kinase receptor normally expressed by the interstitial cells of Cajal. These mutations, primarily at exon 11, rarely at exons 9 and 13, and occasionally at other sites, result in a ligand-independent activation of the receptor, which in turn leads to the detection of CD117 by immunohistochemistry. Although it is felt that GIST is a mesenchymal tumor, the exact cell of origin of this tumor remains undetermined. The interstitial cell of Cajal has been proposed as the cell of origin for GIST, based on their shared reactivity of CD117 and CD34, but this theory has also been challenged. GIST cells can have some differentiation toward a primarily contractile function or a neurallike transmitting function. It is unknown whether GIST tumor cells have the ability to differentiate toward adipose tissue.

Some cases of GIST occur in patients with NF1, and their microscopic appearance was thought to be similar to conventional GISTs. However, recent reports independently suggested that NF1-associated GISTs have unique clinical, phenotypic, and genotypic characteristics: these tumors are likely to be multicentric, to originate in the small bowel, and typically to be composed of spindle cells. Among 69 cases of GISTs associated with NF1, only 6 cases (8.7%) had gastric GISTs. Although most of these GISTs are immunohistochemically reactive for CD117, they usually do not have activating c-kit or PDGFRA mutations; only 3 (3.9%) of 76 GISTs from 36 patients with NF1 showed c-kit mutations in exon 11 or 13, and 2 (2.6%) of 76 GISTs from 36 patients with NF1 had mutations in exon 12 or 18 of PDGFRA. Sometimes, cases of multiple GISTs have developed in the context of the Carney triad,
which also includes pulmonary chondroma and extra-adrenal paragangliomas.11,12 Although previous reports suggested that GISTs in this setting are characteristically multiple and have an epithelioid morphology,14 a mixed spindle and epithelioid morphology or sarcomatous spindle proliferation were observed in one report.15 The GISTs in Carney triad are usually located in the stomach. Multiple GISTs are also associated with paragangliomas and present as a familial syndrome.13 In this association, the GISTs are also located in the stomach. GISTs with neurallike features may sometime present as multiple tumors throughout the gastrointestinal tract in the familial setting of small intestinal neuronal dysplasia, and one case had a germline mutation of the \textit{c-kit} gene.27,28

In our case, most of the GISTs were composed of nodular proliferation of epithelioid cells, but plump spindle cells were noted focally in a few tumors. All of the stained tumors were strongly immunoreactive for CD117, but negative for S100 protein and smooth muscle-specific actin. Because of multicentric nature of the GISTs in our patient, he was evaluated for neurofibromatosis, but no stigmata of that disorder were seen. In addition, the gastric location of all GISTs and the predominance of epithelioid cells within the tumors in our patient were different from the usual picture of GISTs associated with neurofibromatosis.

Lipomas of the intestinal tract are relatively uncommon, benign tumors, arising approximately equally in men and women, who are, most frequently, in their 50s and 60s.29 Gastrointestinal lipomas occur predominantly in the large bowel (64.3%), decreasing in prevalence in the small bowel, stomach, and esophagus.14 The right side of the colon is preferentially affected.14,15 Gastrointestinal lipomas range in prevalence from 0.2% to 5.8% depending on the population of patients in a particular study.14,15 They vary in size and only those measuring more than 2 cm are likely to become symptomatic.29 The most frequent presenting symptoms are abdominal pain, melena, anemia, and intussusception.30–32 The diagnosis can be made by a barium study, computed tomography, and by an endoscopic examination. Lipomas usually present endoscopically as slightly polyloid, submucosal masses with a yellow color. The most characteristic feature of lipomas is the yellow, greasy appearance after incision through the mucosa.

Most lipomas present as a solitary lesion. Multiple lipomas (>4) and lipomatosis are very rare with a reported prevalence of approximately 0.3% in one large autopsy series.15 The diagnostic criteria of lipomatosis used in the literature are not well established; it is not clear how many lipomas need to be present for a diagnosis of lipomatosis. Two cases of symptomatic diffuse colonic lipomatosis were reported.30,31 Catania et al31 reported a lipomatosis case in which more than 100 submucosal sessile and polyloid lipomas throughout the colon were identified, and the same authors found 12 additional cases of diffuse colonic lipomatosis in a review of the literature dating back to 1931, using the criteria of multiplicity and diffuse involvement. Yakabe and Miki31 reported 6 cases of intestinal lipomatosis and reviewed 23 cases, including their own. The age distribution of lipomatosis ranged from 20 to 88 years, with a mean age of 50.7 years (n = 22). The site of lipomatosis usually involves the ileum in 39% of the cases, the jejunum and the ileum in 39% of the cases, and the jejunum in 13% of the cases. Climens and Wylin35 reported 2 cases of intestinal lipomatosis, which contained numerous polyoid submucosal lipomas, and reviewed 16 previously reported cases.

Some patients with lipomatosis or multiple lipomas of the soft tissue have a family history of the disease, suggesting an inherited tendency. Lipomatous lesions in soft tissue are reported to be associated with Proteus syndrome,44 which is caused by a germline mutation of the tumor suppressor \textit{PTEN},20,21 resulting in a variety of cutaneous and subcutaneous lesions including vascular malformations, lipomas, hyperpigmentation, and several types of nevi. Recently, 2 cases of colonic lipomatosis were reported30,32 in pediatric patients with Proteus syndrome. It has been suggested that lipomatous lesions (lipomatosis) in Proteus syndrome show specific histologic features that distinguish them from more typical lipomas: the lack of an obvious vascular component, a lobulated appearance imposed by marked fibrosis, lack of encapsulation, and a diffuse, infiltrative nature.30,34 In rare cases, soft tissue or intestinal lipomatosis is noted in patients with a mutation in the \textit{NFI} gene or in patients with \textit{NF1}.19,39 Our patient had neither signs nor family history of the above-mentioned syndromes and did not have any of the above-mentioned histology in his lipomas. It has also been suggested33 that lipomatosis might be hamartomatous because of the presence of some neural bundles in lipomas. However, in our patient, no neuronal or muscular elements were found in the lipomas. A long-term follow-up of the patient and his family members was, nevertheless, recommended to identify any possible hereditary factors.

It is well recognized that GIST cells can differentiate toward a primarily contractile function or a neurallike transmitting function. A previous report34 of one case of synchronous epithelial stromal tumor and lipoma in the stomach and our current case led us to postulate that GIST cells and lipoma cells may share common genetic abnormalities. However, the GIST cells in our patient showed strong membranous staining for CD117 when tested by immunohistochemistry, but no CD117 immunoreactivity was observed in the lipoma cells. The coexistence of multiple GISTs and multiple lipomas in this patient suggests a common underlying genetic abnormality; the exact genetic alteration remains unknown. The mutation of the \textit{c-kit} gene is not likely to be the direct cause of lipoma. We postulate that an alteration in an upstream signaling molecule upregulates the expression of CD117 in some gastrointestinal stromal cells, leading to the formation of GISTs and the development of lipomas. Although there is a dual association of \textit{NF1} with either GIST or lipomatosis, our patient lacked any signs and had no family history of neurofibromatosis, but genetic evaluation for that syndrome was not done.

In summary, we describe the synchronous presence of multiple gastric GISTs and intestinal lipomatosis in a 36-year-old man. Although both multiple GISTs and gastrointestinal lipomatosis have been reported to be occasionally associated with a few genetic syndromes, there is no report, to our knowledge, regarding their coexistence. We feel that the coexistence of multiple lesions of these 2 rare diseases in this relatively young patient may represent a novel syndrome.

References


