Summary: An 81-year-old man initially presented with a right forearm mass that was found to be myxofibrosarcoma. In addition, he was found to have gastric and intragastric masses identified as neuroendocrine tumor (NET) and gastrointestinal stromal tumor (GIST; presenting synchronously), respectively, as well as a new left upper quadrant mass identified as desmoid tumor in the colon. The patient complained of melena, which was found to be due to metastatic myxofibrosarcoma in the transverse colon. Several reports have associated GIST with NET and some reports have associated GIST with sarcomas and NET with sarcomas; however, this is the first report to document all these tumors in a single patient. Several factors may have contributed to the development of these tumors, including growth factors secreted by NET, KIT mutation of GIST predisposing to additional tumors, immunosuppressed state, or an underlying genetic syndrome. This case highlights the importance of investigating for additional malignancies when a primary malignancy is discovered.

Case Report

An 81-year-old man with a past medical history significant for multifocal lipomas and prostate cancer, for which he underwent prostatectomy, presented for removal of a mass on his right forearm. Excision was performed and pathology revealed high-grade myxofibrosarcoma. The resected tumor was 5 cm in size. Histologically, the tumor was poorly differentiated and involved the surgical resection margins. The tumor was composed of large epithelioid cells and spindle cells with scattered multinucleated cells. Nuclear pleomorphism was present, and the surrounding stroma was myxoid and desmoplastic. The patient underwent wide resection and radiotherapy.

Positron emission tomography/computed tomography demonstrated a large, hypermetabolic, soft-tissue mass in the subcutaneous fat of the posterior thigh and a hypermetabolic mass in the left upper quadrant of the abdomen. Wide excision of the mass of the posterior thigh revealed a 6-cm, metastatic, high-grade myxofibrosarcoma with positive margins. The patient underwent radiotherapy.

Later the same year, the patient underwent esophagogastroduodenoscopy, which revealed a gastric mass seen at the greater curvature; partial gastrectomy was performed. Macroscopically, a 5.5 × 3.2 × 3.2 cm well-circumscribed, soft, tan-colored, lobulated gastric mass was identified. The tumor was composed of a monomorphic population of cells with granular pink cytoplasm and round vesicular nuclei with nucleoli (Fig 1A). Immunohistochemically, the tumor was diffusely positive for cytokeratin (Fig 1B), chromogranin, and synaptophysin (Fig 1C), and Ki-67 revealed 4% positivity in 4% of the tumor (Fig 1D). These findings supported a diagnosis of well-differentiated, grade 2 neuroendocrine tumor (NET). One of 4 regional lymph nodes was positive for metastatic NET.

In addition, a 2.5 × 1.3 × 1.1 cm, well-circumscribed, firm, tan-colored intragastric mass composed of spindle cells, arranged in intersecting fascicles and focally exhibiting paranuclear vacuoles (Fig 2A), was seen. These cells were diffusely positive for CD117 (Fig 2B) and CD34 (Fig 2C) but negative for actin (Fig 2D) and S100 by immunohistochemistry. The Ki-67 proliferation index was 1%. Genetic analysis of the mass revealed a mutation in exon 11 of KIT. Based on these findings, the diagnosis of gastrointestinal stromal tumor (GIST) was made.

More than 2 years after the patient originally presented, computed tomography of his abdomen and pelvis showed a new mass in the left upper quadrant of his abdomen, so segmental colectomy with primary colocolostomy was performed. The tumor was 3 cm in its largest diameter and had negative margins. Gross examination revealed a white, dense mass invading the muscularis propria of the large bowel. Microscopically, the tumor was composed of plump, fibroblastic spindle cells infiltrating the smooth muscle of the muscularis propria (Fig 3A). No necrosis or mitotic activity was present. The lesion was completely resected. The lesional cells were immunohistochemically positive for beta-catenin (Fig 3B) and negative for S100, CD117, ac-
tin, and desmin. These results supported the diagnosis of a desmoid tumor (fibromatosis).

Nine months later, the patient represented with melena, and subsequent colonoscopy revealed a polypoid lesion in the transverse colon measuring 3.5 cm in its largest diameter. Histologically, the tumor was similar to this patient’s primary high-grade myxofibrosarcoma located in his right forearm and had infiltrated the colonic wall, including the colonic mucosa (Fig 4).

**Discussion**

GISTs have been well documented to be associated with the development of synchronous primary tumors, and this rate of association can be as high as 11.5% to 33.3%. Oftentimes, GIST coexists with adenocarcinoma of gastric, colonic, or pancreatic origin, as well as breast, prostate, and lung cancers.2,5

In our patient, GIST was found in association with gastric NET, a finding that has been reported a handful of times. In 1 case report, a 69-year-old man with well-differentiated NET in the corpus was also found to harbor submucosal borderline GIST.4 In another case, a 65-year-old woman with GIST of the gastric corpus was diagnosed with concomitant, well-differentiated NET in the same location.5 Although these 2 cases are examples of GIST being synchronous to NET, other cases have described a single tumor type that predated the occurrence of the second tumor by years; however, no clear predisposition of one tumor leading to the other has been established.2,6

GISTs have also been found in association with sarcomas. Arniogiannaki et al1 reported the simultaneous occurrence of gastric GIST with uterine leiomyosarcoma. Similarly, Sharma et al7 reported a case of a 50-year-old woman with ileal GIST and synchronous, high-grade breast sarcoma with heterologous cartilaginous, osseous, and rhabdomyoblastic differentiation. An association with NET and sarcoma has also been described by Adams et al8 who reported the occurrence of embryonal rhabdomyosarcoma of the cervix and appendiceal carcinoid tumor in a 43-year-old woman. However, our patient had a unique combination of myxofibrosarcoma, GIST,
NET, and desmoid tumor. To our knowledge, no other case of this kind has been previously reported in the English literature.

Several hypotheses have been postulated to explain the development of synchronous and metachronous primary tumors in the same patient. Two studies were unable to establish an immunohistochemical or molecular profile difference between single GISTs and GISTs coexisting with other tumors.\(^1\),\(^3\) The secretion of growth factors from NETs could contribute to the development of concurrent primary tumors. Growth factors such as platelet-derived growth factor, transforming growth factor \(\beta\), and basic fibroblast growth factor are secreted from NETs and are all tumorigenic.\(^9\) GISTs are characterized by the \(KIT\) mutation that may predispose them to the development of other tumors; moreover, impaired \(KIT\) expression has been noted in carcinomas of the breast and colon.\(^3\) In addition, a primary malignancy may create an immunosuppressed state, thus causing patients to be more susceptible to developing secondary tumors.\(^10\)

The presence of genetic mutations could also lead to the simultaneous occurrence of these tumors, similar to how cancer syndromes like Li–Fraumeni syndrome, von Hippel–Lindau syndrome, and multiple endocrine neoplasia syndromes result from genetic mutations. Exposure to carcinogenic agents might also lead to the development of these synchronous tumors or, possibly, the synchrony happened by pure coincidence.\(^3\)

**Conclusion**

Gastrointestinal stromal tumors (GISTs) tend to present with synchronous tumors. When a patient is diagnosed with a non-GIST malignancy, the health care professional must consider the possibility of a synchronous or metachronous GIST, among other types of tumors. More research is needed on the pathophysiology of these synchronous and metachronous tumors.

**References**