Calcifying Fibrous Tumor of the Gastrointestinal Tract

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Calcifying fibrous tumor (CFT) is a rare benign mass lesion first described in 1988 by Rosenthal and Abdul-Karim as “childhood fibrous tumor with psammoma bodies.”1 Fetsch and colleagues published a larger series, redesignating the lesion as “calcifying fibrous pseudotumor.”2 While originally described as a soft tissue tumor in children, CFT has since been documented in a wide age range and in a variety of sites, including soft tissue, solid organs, associated with pleural and peritoneal surfaces, and the tubular gastrointestinal (GI) tract. A review of the English-language literature reveals 43 such reports of GI CFTs. Clinical signs, imaging studies, and endoscopic findings are nonspecific. Although uncommon, pathologists must be aware that CFTs may occur in the GI tract to differentiate it from other potentially more aggressive, rare mesenchymal lesions.


Califying fibrous tumors are predominantly submucosal and range from 0.5 to 11.0 cm in maximum dimension, with an average size of 2.6 cm. Macroscopically, they are well-demarcated, unencapsulated, spherical to lobulated masses with a solid and white to gray cut surface. They have a firm texture and often a gritty sensation during sectioning. Yellow calcifications are sometimes grossly identifiable. Microscopically, CFT is defined by the following components: (1) abundant, paucicellular, hyalinized collagen; (2) interspersed calcifications; and (3) an inflammatory infiltrate. The collagenous matrix often exhibits a whorled or storiform pattern but may be haphazard or patternless (Figure, A).3,6,17,21 Bland spindle cells are embedded within the abundant collagen. The spindle cells exhibit ovoid, vesicular nuclei with fine chromatin and inconspicuous nucleoli and abundant eosinophilic to amphophilic cytoplasm. Atypia and mitotic figures are lacking. The calcified component, dispersed throughout the fibrotic areas, may be either psammomatous or dystrophic (Figure, B). The inflammatory component is predominantly composed of lymphocytes and plasma cells infiltrating singly or forming aggregates (Figure, C).13,19 Germinal centers may be present; these germinal centers may show central hyalinization.31 A lymphoplasmacytic cuff is sometimes notable at the tumor margin.

GROSS AND MICROSCOPIC PATHOLOGY

Most GI CFTs are the subject of single-case reports. Only a few case series exist. The most commonly involved sites are the stomach3–16 and small intestine.3,4,6,14,17–25 Three examples in the large intestine exist14,17,26 and a single case in the esophagus.27 Patient age ranges from 5 to 77 years, with a mean of 40.8 years; no sex predilection is evident. Multiple lesions were documented in 11 of 43 patients, many of which had concurrent extra-GI involvement, with the most common site being the mesentery.14,17,19,20,22–25 One author reported GI CFTs occurring in siblings.19 Although most are discovered incidentally, CFTs in the GI tract can present in unique ways. Three gastric CFTs manifested as gastric ulcers.11–13 Three patients with small intestinal CFTs and concurrent mesenteric nodules were seen with obstruction.17,19,24 Two other small intestinal cases presented with intussusception,20,21 Some simply manifest as abdominal or epigastric pain.

Only rare reports of GI CFTs contain well-documented imaging findings. Endoscopic ultrasonography may reveal a hypoechoic mass with internal hyperechoic calcifications.27 If imaged by computed tomographic scan, a well-circumscribed, homogeneous mass with mild enhancement and scattered calcifications may be identified.13,16,23,24,27 One study7 describes magnetic resonance imaging findings as isosignal intensity on gadolinium-enhanced T1-weighted imaging and as hypointensity on T2-weighted imaging. On direct or endoscopic visualization, most are recognizable as subserosal or submucosal nodules. Five gastric CFTs have been noted as polyoid on endoscopy.5,7,13,16

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Scattered mast cells and eosinophils have also rarely been noted. Although generally well circumscribed, CFTs are unencapsulated and may extend between layers of the GI tract wall, splaying apart muscle bundles. Peripheral entrapment of small nerves and adipocytes is only rarely described.

**ANCILLARY STUDIES**

By definition, CFT is a morphologic diagnosis, but ancillary studies may be applied to exclude alternative diagnoses. Immunohistochemically, the spindle cells stain strongly and diffusely for vimentin and factor XIIIa (Figure, D). Reactivity with other immunostains, including smooth muscle actin, CD68, desmin, and CD34, is variable and often patchy. Recent studies have also highlighted that many of the plasma cells in CFT are positive for IgG and IgG4.

The only molecular study published showed that 5 gastric CFTs harbored no mutations in KIT exons 9, 11, 13, and 17 or PDGFRA exons 12, 14, and 18. Electron microscopy performed on a series of non-GI CFTs has shown that the spindle cells are fibroblasts in various stages of differentiation, which supports the immunohistochemical findings of variable positivity for fibroblastic and myofibroblastic markers.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for GI CFTs predominantly includes spindle cell mesenchymal lesions and inflammatory conditions. The mesenchymal neoplasms that most commonly enter the differential diagnosis include GI stromal tumor (GIST), schwannoma, hyalinized leiomyoma, and solitary fibrous tumor. Tables 1 and 2 summarize the differential morphologic and immunohistochemical features of these entities. Less common diagnostic mimics include inflammatory myofibroblastic tumor (IMT), reactive nodular fibrous pseudotumor, fibromatosis, Gardner fibroma, sclerosing mesenteritis, and amyloidoma.

Like CFTs, GISTs may be paucicellular and (rarely) calcified. In contrast to CFTs, however, GISTs are generally composed of fascicles of elongated spindle cells with a fibrillary stroma. The use of CD117 immunohistochemistry in most GISTs is normally sufficient to delineate the 2 entities because the spindle cells are negative for CD117 in CFTs.* CD34 immunostaining can be confusing, al-

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* References 7, 9, 12, 13, 15, 16, 20, 24, 25, 27.
though positivity in CFTs is weak and patchy compared with the strong diffuse staining in GISTs.

Schwannomas may also mimic CFT by their paucicellularity, areas of hyalinization and calcification, and peripheral lymphoid aggregates. However, the spindle cells of schwannomas have characteristic undulating nuclei and are arranged around eccytic, hyalinized vessels in a variably myxoid extracellular matrix. The CFTs may have scanty extracellular mucin, but their stroma is abundantly collagenous. Strong diffuse S100 positivity supports a nerve sheath origin and excludes CFT.

Leiomyomas may be quite paucicellular, hyalinized, and extensively calcified. However, the fascicular architecture and fusiform tumor cell nuclei of leiomyomas are usually sufficient to make the diagnosis. When in doubt, immunohistochemical staining for desmin, smooth muscle actin, and caldesmon may help to resolve the dilemma. At least 2 of the 3 are typically diffusely and strongly positive in leiomyomas, in contrast to the variable weak reactivity noted in a subset of CFTs.

Solitary fibrous tumor may resemble CFT, depending on the degree of cellularity and hyalinization. Morphologically, the spindle cells of solitary fibrous tumor are elongated with pink cytoplasm. They are arranged within a densely hyalinized stroma with distinctive intervening hemangiopericytic vasculature. Solitary fibrous tumor is invariably CD34 positive. Most tumors also show reactivity for BCL-2 and CD99, which is not described in CFT.

The histologic presentation of CFT can be very similar to IMT because IMT may be paucicellular and densely collagenous, contain a lymphocytic infiltrate, and (rarely) include calcifications. In its most common manifestation, IMT is a cellular spindle cell proliferation with a myxoid stroma and prominent mixed inflammatory background composed of lymphocytes, histiocytes, neutrophils, and occasional eosinophils. The spindle cells havestellate nuclei and pinpoint nucleoli. A myxoid stroma is invariably present. Smooth muscle actin is uniformly positive in a myofibroblastic pattern but only variably and weakly positive in CFT. Rarely, CFT and IMT have been described as coexisting in the same patient in close proximity, leading some to suggest that CFT could be a late sclerosing stage of IMT.\textsuperscript{10,17} However, with the discovery of rearrangements of the ALK gene and ALK-1 immunohistochemical positivity in a large subset of IMTs, IMT is now widely regarded as a truly neoplastic process. Calculifying fibrous tumor is uni-

| Table 1. Histologic Features of Calculifying Fibrous Tumor and Common Differential Diagnoses |
|-------------------------------------------|---------------------------------|----------------|----------------|----------------|----------------|
| **Histologic Feature**                    | **Calculifying Fibrous Tumor**  | **Leiomyoma** | **Schwannoma** | **Gastrointestinal Stromal Tumor** | **Solitary Fibrous Tumor** |
| Cellularity                               | Hypocellular                    | Hypocellular  | Alternating cellular and hypocellular areas | Cellular | Alternating cellular and hypocellular areas |
| Stroma                                    | Abundant hyalinized collagen    | Variable hyalinization, myxoid change | Myxoid areas | Varying myxoid | Prominent hyalinization, variably myxoid |
| Architecture                              | Scattered single cells, may be vaguely storiform | Short intersecting fascicles | Short fascicles | Fascular or storiform | Patternless myxoid |
| Inflammation                              | Lymphoplasmacytic infiltrate, variable germinal center formation, variable perilesional cuff | Not prominent | Lymphoplasmacytic infiltrate, periilesional cuff | Not prominent | Not prominent |
| Calcification                             | Essential                       | Occasionally prominent | Occasionally prominent | Unusual | Not prominent |
| Vasculature                               | Not prominent                   | Not prominent | Large vessels, perivasular hyalinization, fibrin thrombi | Not prominent | Large vessels, prominent branching, perivasualar hyalinization |
| Nuclei                                    | Ovoid, vesicular, no atypia     | Elongated, blunt-ended, paranuclear vacuoles, no atypia | Wavy to ovoid, variable intranuclear vacuoles, prominent palisading, no atypia | Elongated to ovoid to epithelioid, rare palisading, rarely atypical |

| Table 2. Immunohistochemistry of Calculifying Fibrous Tumor and Common Differential Diagnoses |
|---------------------------------------------|---------------------------------|----------------|----------------|----------------|----------------|
| **Immunostain**                             | **Calculifying Fibrous Tumor**  | **Leiomyoma** | **Schwannoma** | **Gastrointestinal Stromal Tumor** | **Solitary Fibrous Tumor** |
| Factor XIIIa                               | +                               | NA             | NA             | NA             | NA             |
| CD34                                       | ±                               | NA             | NA             | ±              | ±              |
| CD68                                       | ±                               | ±              | NA             | NA             | ±              |
| CD68 (focal)                               | +                               | NA             | ±              | ±              | ±              |
| Smooth muscle actin                       | +                               | ±              | NA             | ±              | ±              |
| Desmin (focal)                             | NA                              | ±              | NA             | ±              | ±              |
| Caldesmon (focal)                          | +                               | NA             | NA             | NA             | NA             |
| S100                                       | ±                               | NA             | ±              | ±              | ±              |
| CD117                                      | +                               | NA             | ±              | ±              | ±              |
| DOG-1 (nuclear)                            | ±                               | NA             | ±              | ±              | ±              |

Abbreviations: NA, not applicable; +, positive; −, negative; ±, may be positive or negative.
formally negative for ALK-1 and has never been shown to have recurrent cytogenetic abnormalities.\textsuperscript{5,19}

Reactive nodular fibrous pseudotumor is another rare, paucicellular, fibroblastic proliferation that manifests in the GI tract with nonspecific symptoms. Like CFT, it is composed of hypocellular nodules of hyalinized stroma and may have a prominent lymphoid cuff. However, reactive nodular fibrous pseudotumor has an infiltrative border and is composed of stellate and spindled fibroblasts arranged in a haphazard fashion, admixed with small lymphocytes. A myxoid stroma may be present. Actin is positive in reactive nodular fibrous pseudotumor and may be positive in CFT, but the spindle cells of reactive nodular fibrous pseudotumor are frequently positive for CD117 as well.\textsuperscript{20}

Fibromatosis has a distinctive appearance both grossly and microscopically. Grossly, fibromatosis is poorly circumscribed, and the bulk of the lesion involves the abdominal wall or mesentery, only secondarily involving the luminal GI tract. Calcifying fibrous tumor may arise from virtually anywhere in the abdomen, including the abdominal wall, mesentery, and luminal GI tract, but only rare cases have not been well circumscribed.\textsuperscript{12,22,23} Fibromatosis is infiltrative and composed of long, sweeping fascicles of elongated spindle cells. Although keloidal collagen is frequently present in fibromatosis, the fascicular arrangement of the spindle cells of fibromatosis morphologically distinguishes it relatively easily from CFT. In most cases, β-catenin is expressed in the nuclei of the spindle cells of fibromatosis and not in those of CFT.

Gardner fibroma is far less common than fibromatosis but may prove more difficult to delineate from CFT by virtue of its circumscription, hyalinization, and paucicellularity. Like fibromatosis, Gardner fibroma more commonly primarily involves abdominal structures other than the luminal GI tract. In general, it lacks plasma cell infiltrates and calcifications. By immunohistochemistry, Gardner fibroma is strongly positive for CD34 and exhibits nuclear expression of β-catenin.\textsuperscript{20}

Sclerosing mesenteritis may involve the bowel wall, just as poorly circumscribed CFTs may adhere to the mesentery.\textsuperscript{3,22,24} The gross inspection again becomes critically important in such cases to determine the lesion as primarily or secondarily involving the mesentery. On histologic examination, sclerosing mesenteritis may closely resemble CFT in that both are paucicellular and fibrotic and contain a lymphoplasmacytic infiltrate. Differentiating characteristics include calcifications, which are absent in sclerosing mesenteritis. In addition, the fibrosis in sclerosing mesenteritis typically envelopes adipocytes, and fat necrosis frequently ensues. Envelopment of adjacent structures has only rarely been associated with GI CFTs.\textsuperscript{12} Immunohistochemical characterization of sclerosing mesenteritis is limited, but smooth muscle actin is positive.

If inflammatory infiltrates and calcifications are inconspicuous, the abundant eosinophilic stroma of CFT can resemble amyloid. However, amyloidoma is typically even less cellular than CFT, and the matrix of CFT is negative when stained for amyloid.\textsuperscript{2,3,24}

Several authors have noted a high number of IgG4-positive plasma cells in CFT, leading some to speculate that it may be part of the spectrum of IgG4-related disease.\textsuperscript{25} IgG4-related lesions are characterized histologically by dense storiform fibrosis, lymphoplasmacytic infiltrate, and obliterator phlebitis. They also often have a high number of IgG4-positive plasma cells, a high ratio of IgG4-positive to IgG-positive plasma cells, and elevated serum IgG4, although these findings are not specific to IgG4-related disease. By definition, CFT consists of dense fibrosis. However, inflammatory infiltrate is generally of a lesser degree than in IgG4-related lesions, andobliterator phlebitis is not a feature of CFT. IgG4-related disease also responds to corticosteroid therapy, which has never been shown to be effective for CFT. There are also numerous examples of multifocality in CFT, which is not characteristic of IgG4-related disease. Although they bear some features in common, a definitive connection between CFT and IgG4-related disease has yet to be convincingly demonstrated.

**TREATMENT AND PROGNOSIS**

Treatment of CFT is primarily aimed at addressing symptoms (obstruction, intussusception, etc.). Calcifying fibrous tumor of the esophagus has been treated by excision.\textsuperscript{27} Calcifying fibrous tumors in the stomach have been treated by wedge resection.\textsuperscript{3,9,15,16} Intestinal examples have been predominantly treated by segmental resection, although enucleation has also been performed.\textsuperscript{21} Calcifying fibrous tumor is considered benign and cured by local removal, although rare recurrences have been noted in extra-GI lesions.\textsuperscript{6} While multifocal CFTs have been described, there have been no documented cases of metastatic disease.\textsuperscript{14,17,19,20,22-25}

**CONCLUSION**

Calcifying fibrous tumor has been predominantly thought of as a tumor of the deep soft tissues. However, a thorough review of the literature reveals 43 cases of this tumor involving the GI tract, indicating that it may not be as rare in this location as previously thought. Clinical and imaging findings are nonspecific and effectively noncontributory to the diagnosis. Definitive diagnosis is made by histology, where the lesion is defined by the aforementioned triad of dense fibrosis, inflammation, and interspersed calcifications. Although the histologic diagnosis is theoretically straightforward, pathologists should be aware of CFT as a differential diagnosis when considering other mesenchymal lesions in the GI tract.

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**References**


