Soft Tissue Giant Cell Tumor of Low Malignant Potential

The term soft tissue giant cell tumor of low malignant potential (STGCTLMP) has recently been proposed to designate the equivalent in soft tissues of giant cell tumor of the bone.1–7 Most probably, before being classified as an independent specific neoplasm, examples of STGCTLMP were included among giant cell tumors of the tendon sheath, malignant giant cell tumors of soft tissue (giant cell type of malignant fibrous histiocytoma), plexiform fibrohistiocytic tumors, or even epithelioid sarcomas.

CLINICAL FEATURES

STGCTLMP most commonly develops in the subcutaneous tissue of the extremities, particularly on the arms, hands, or feet (Fig. 27-1). The lesion presents in adults, showing no gender preference. Clinically, the lesion consists of multiple nodules grouped in a plaque that diffusely infiltrates into the subcutaneous tissue of the affected region. There are cases in which the lesions affect exclusively the dermis;8,9 involvement of internal organs, including the breast, salivary glands, pancreas, lung, kidney, and nasal cavity, has also been described.10

HISTOPATHOLOGIC CHARACTERISTICS

Tumor nodules are made up of monomorphous mononuclear cells with a vesicular nucleus and small nucleolus, spindle cells, and osteoclast-like multinucleated giant cells (Fig. 27-2). Unlike in the giant cell type of malignant fibrous histiocytoma, mononuclear and multinucleated giant cells of STGCTLMP do not exhibit marked atypia, although mitotic figures are seen. As in giant cell tumors of the bone, there is vascular invasion in approximately half of STGCTLMP cases, but usually without necrotic areas. Areas of bone metaplasia can also be seen, sometimes forming an osseous ring around the tumor and dilated vascular spaces resembling aneurysmal bone cysts.

Immunohistochemically, mononuclear cells of STGCTLMP express CD68 and smooth muscle actin, while osteoclast-like multinucleated giant cells are positive for the osteoclast marker tartrate-resistant acid phosphatase, but no expression is seen for CD45, S100 protein, desmin, or lysozyme.4 Recently, immunoreactivity for p63 in the nuclei of neoplastic cells of STGCTLMP has been described,11 but no cytogenetic abnormalities have been yet identified in samples of STGCTLMP.12

TREATMENT

Surgical excision is the treatment of choice. STGCTLMP has better biologic behavior than giant cell–type malignant fibrous histiocytomas of soft tissue. Approximately 20% of STGCTLMP recur after incomplete surgical resection; however, an aggressive biologic course occurred with metastasis to the parotid gland only in one immunosuppressed patient 12 years after heart transplantation.11 Two additional cases of STGCTLMP developed lung metastases;12–14 the latter case was a patient with breast STGCTLMP that developed lung metastases, causing the death of the patient 1 year after its clinical presentation despite surgical resection with wide margins of the primary lesion.14
REFERENCES


FIGURE 27-2. Histopathologic characteristics of STGCTLMP. A: Panoramic view showing two relatively well-defined nodules in the dermis. B: Cystic spaces containing red cells can be seen at the periphery of the largest nodule. C: Neoplastic nodules are composed of monomorphous mononuclear cells with vesicular nuclei, inconspicuous nucleoli, and osteoclast-like multinucleated giant cells. D: Detailed image of multinucleated giant cells.
Inflammatory myofibroblastic tumor was originally described as a pediatric lung neoplasm, but it was later shown that it can occur in any site including subcutaneous soft tissues. Many other terms have been used in the literature when describing this tumor, such as plasma cell granuloma, plasma cell pseudotumor, inflammatory myofibrohistiocytic proliferation, omental–mesenteric myoid hamartoma, and, the most common, inflammatory pseudotumor. The term inflammatory myofibroblastic tumor is preferable to inflammatory pseudotumor, because the latter has been used to designate very different lesions, including pseudosarcomatous myofibroblastic proliferations of the genitourinary tract, atypical mycobacterial infections, dendritic cell tumors of the liver or spleen associated with Epstein-Barr virus, and reactive inflammatory pseudotumors of lymph nodes.

**CLINICAL FEATURES**

Inflammatory myofibroblastic tumors have been described in almost all anatomical sites, including cases in which the lesions are exclusively cutaneous (Fig. 28-1). Although it can appear at any age, these tumors mainly occur during childhood, with a mean age of 10 years, and they seem to occur slightly more often in girls than boys. Although the etiology of this tumor is unknown, the possible role of certain viruses in the etiopathogenesis has been suggested, including the HHV-8 and the Epstein-Barr virus. A cytokine production pattern has been shown in some cases, suggesting that the lesion is more a reactive than a neoplastic process; external injuries have also been postulated as an etiologic factor.

Symptoms depend on tumor location. In soft tissues, the lesion presents as a slow-growing, ill-defined tumor, causing only slight local discomfort. However, and particularly in extracutaneous cases or with multiple lesions, the affected patients frequently suffer from tumor-related general symptoms, including fever, general discomfort, night sweats, and weight loss. Furthermore, laboratory results indicate anemia, elevated erythrocyte sedimentation rate, thrombocytosis, and hypogammaglobulinemia. The previously described symptoms and the abnormal laboratory results disappear once the tumor is removed. It can resemble other malignant neoplasms, has a high risk of recurrence, and can even cause paraneoplastic syndromes such as paraneoplastic pemphigus.

**HISTOPATHOLOGIC CHARACTERISTICS**

At scanning magnification, inflammatory myofibroblastic tumors exhibit a multilobular architecture, but the entire lesion is well demarcated. The histopathologic findings in inflammatory myofibroblastic tumors vary depending on the case and between different areas within the same tumor. Some cases are made up of spindle or stellate cells immersed in a myxoid or hyaline stroma with a scattered inflammatory infiltrate of lymphocytes. In these cases, the lesion resembles a nodular fasciitis. By contrast, other cases are made up of solid aggregates of spindle cells with a vesicular nucleus and eosinophilic cytoplasm, arranged in a storiform or fascicular pattern. In these solid aggregates, the nuclei of neoplastic cells are elongated without atypia, hyperchromatism, or nuclear pleomorphism. These solid aggregates are usually surrounded by nodules of the inflammatory lymphoplasmacytic infiltrate, occasionally with germinal centers, primarily found in the periphery of the lesion (Fig. 28-2), and by a proliferation of venules lined by prominent endothelial cells. In other areas, the lesion is made up of isolated spindle cells in a sclerotic stroma resembling the histopathologic pattern of a scar. A scattered lymphoplasmacytic
infiltrate throughout the lesion is also seen in these cases, and small calcification points or osseous metaplasia is not uncommon. Sometimes, cells with xanthomatous cytoplasm are seen. In some lesions, there is more cytologic atypia with neoplastic cells exhibiting a large nucleus and a noteworthy nucleolus. The presence of large histiocyte-like cells has been described in other cases, resembling ganglion cells or Reed-Sternberg cells.

Immunohistochemically, tumor cells strongly express vimentin, while the expression for smooth muscle actin, muscle actin, and desmin varies among cases. Focal cytokeratin expression is also seen in some cases. The lymphocytes in the infiltrate are a mixture of T and B cells, plasma cells are polyclonal, and expression of kappa and lambda light chains occurs. Although plasma cells of inflammatory myofibroblastic tumors express IgG4 in variable proportions, this lesion is not included in the spectrum of IgG4-related diseases.

Ultrastructural observations reveal that most inflammatory myofibroblastic tumor cells exhibit myofibroblastic features, with abundant rough endoplasmic reticulum, a prominent Golgi apparatus, intracytoplasmic filaments, dense bodies, and junction complexes.

Several translocations have been shown in inflammatory myofibroblastic tumor, particularly involving chromosomal band 2p22-24. The gene for anaplastic lymphoma kinase (ALK), localized at 2p23, has been associated with the pathogenesis of this tumor. Anaplastic lymphoma kinase (ALK) codes for a tyrosine kinase receptor, member of the superfamily of the insulin-like growth factor receptor. In the majority of inflammatory myofibroblastic tumors, particularly in childhood and in young adults, albeit quite rarely in adults over 40 years of age, the 3' kinase region of the ALK gene fuses with one of various partner genes including TPM3, TPM4, CLTC, ATIC, and RANBP2, which results in characteristic
translocations and fusion genes: t(1;2)(q22:p23) with TPM3–ALK fusion, t(2;19)(p23;q13) with TPM4–ALK fusion, t(2;17) (p23;q23) with CLTC–ALK fusion, t(2;2)(p23;q35) with ATIC–ALK fusion, and t(2;2)(p23;q13) with RANBP2–ALK fusion.19–28 Remarkably, various other tumors, including lymphomas and leukemias, may harbor identical fusion genes. The SEC31L1–ALK fusion gene resulting from t(2;4) (p23;q21) has recently been described in intraabdominal inflammatory myofibroblastic tumor.43 In neoplastic cells harboring one of the various gene fusions, different ALK immunostaining patterns may be encountered, including diffuse cytoplasmic staining, cytoplasmic granular staining, membrane staining, or nuclear staining.38,44–46 There also seems to be a relationship between cytogenetic findings and prognosis. The presence of the RANBP2–ALK fusion gene has been linked with the transformation to round cells, ALK expression in the nuclear membrane, and a worse prognosis.28 Lack of ALK expression has been associated with tumor appearance at a later age, higher nuclear pleomorphism, cellular atypia, and atypical mitoses, as well as a higher risk of developing distant metastases and death.28 For diagnostic purposes, ALK immunostaining and ALK split-apart FISH are of particular importance.

TREATMENT

Extraabdominal inflammatory myofibroblastic tumors are less aggressive than are lesions located in the abdomen or the retroperitoneum. It seems that cases with greater cytologic atypia, neoplastic cells similar to ganglion cells, higher p53 expression, and aneuploidy are those with more aggressive biologic behavior.48 In cases with multiple lesions, it is not clear whether the origin is multifocal or they are authentic metastases. Surgical excision is the treatment of choice, even in the case of recurrence. Some authors have recommended chemotherapy or radiation therapy for recurrent or metastatic cases.49,50

In some cases, there were reports on successful therapy with nonsteroidal anti-inflammatory drug infusions, such as ketorolac or COX-2, alone or in combination with corticosteroids, nonsteroidal anti-inflammatory drug infusions, such as ketorolac or COX-2, alone or in combination with corticosteroids, and radiation therapy for recurrent or metastatic cases.49,50

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