Sclerosing epitheloid fibrosarcoma. A report of two cases

Fibrosarcoma epitelioide sclerosante. Descrizione di due casi

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Summary
Sclerosing epitheloid fibrosarcoma is a rare, histologically well-defined member of adult fibrosarcoma group of soft tissue tumors. Its main histological features are nests and cords of rounded tumor cells surrounded by hyalinized collagenous stroma. Epitheloid appearance with marked sclerosis and infiltrating growth pattern, along with occasional immunohistochemical positivity for epithelial markers may be highly suggestive of infiltrating carcinoma. Despite of bland cytological features clinical course is often protracted with a high local recurrence rate and late metastases. In this report, we present histopathological characteristics of two cases of sclerosing epitheloid fibrosarcoma, together with their clinical presentation, follow-up information and differential diagnosis.

Introduction
For many years, fibrosarcoma was a frequent histopathological diagnosis because it was broadly defined as a sarcoma showing collagen production. At the present time fibrosarcoma is essentially diagnosis of exclusion reserved for those soft tissue tumors composed of spindle cells that immunohistochemically express no other marker than a vimentin. Though relatively rare in times of immunohistochemistry and ultrastructural analysis, well defined histological variants of fibrosarcoma are still present1 2. We have presented here two cases of sclerosing epitheloid fibrosarcoma (SEF) which is clinicopathologically distinct member of the adult fibrosarcoma group.

Clinical cases

CASE 1
A 62 years old man with a painful mass in the thenar region of the right hand, first observed at the end of 1995. In January 1996 a wide surgical tumor excision was performed. During the surgical procedure a tumor infiltration of two digital nerves was observed. On gross inspection tumor represented a well-circumscribed, partially cystic gray-white mass of 4 cm in diameter. The first recurrence forming a solid, lobular, white-gray tumor of 3,5 cm in diameter, in the area of surgical scar was documented in September 1996, when reexcision was performed. The second recurrence in the same area was observed in January 1997, when wide surgical excision of thenar region with thumb amputation was made. This time tumor was poorly circumscribed white

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subcutaneous mass measuring 4 cm in its longest diameter. Patient died in 2000 with clinically documented lung and bone metastases.

**CASE 2**
A 34 years old woman presented with painful subcutaneous tumor located in the left humeral region at the beginning of 2001. Symptoms had been present several months prior to the surgical procedure. A wide surgical excision was performed. Grossly, the tumor was a well circumscribed nodular white-gray mass, measuring 2 cm at its longest diameter. The patient is now well and without signs of locally recurrent disease.

The excised tumors were fixed in a buffered formalin, dehydrated, and embedded in paraffin. Sections were routinely stained with haematoxylin-eosin. The streptavidin-biotin peroxidase technique was employed for immunohistochemical stains, using monoclonal antibodies directed against the following antigens: vimentin, cytokeratin, epithelial membrane antigen, S-100 protein, desmin, smooth muscle actin, neuron specific enolase (NSE) and CD 68 (all provided by DAKO, Glostrup, Denmark). Microscopically, both tumors were almost identical, relatively well circumscribed, with pushing rather than infiltrating margins. They were composed of uniform and relatively small round to ovoid epitheloid cells arranged in nests and cords, and set in an extensive, hyalinized stroma (Fig. 1). Tumor cells had round and oval nuclei with finely stippled chromatin and small basophilic nucleoli. The cytoplasm was clear or eosinophilic (Fig. 2). In the third recurrence of the first case the areas with more cellular pattern of conventional fibrosarcoma with myxoid foci were present (Fig. 3). Polymorphism was minimal and mitotic figures were rare with up to five mitoses per 10 hpf. Immunohistochemically tumor cells showed a strong cytoplasmatic positivity to vimentin. In the second case we noticed an occasional week positivity with EMA. Tumor cells were uniformly negative for cytokeratin, smooth-muscle actin, desmin, CD-68, and neural markers S-100 protein, and NSE.

**Discussion**
With the introduction of immunohistochemistry, electron microscopy and cytogenetic methods in diagnostic pathology of soft tissue tumors, diagnosis of fibrosarcoma has become rarity. The greatest number of fibrosarcomas diagnosed in past would be classified now as monophasic synovial sarcoma, malignant peripheral nerve sheath tumor or malignant fibrous histiocytoma. In spite of this well-defined histological forms of adult-type fibrosarcoma have been recognized: a myxoid type (myxofibrosarcoma), a low-grade fibromyxoid type (Evan’s sarcoma), a hyalinizing spindle cell tumor with giant rosettes and sclerosing epitheloid type (SEF). Fletcher added to this group the acral myxoinflammatory fibroblastic sarcoma, also known as inflammatory myxohyaline tumor of the distal extremities with virocyte or Reed-Sternberg-like cells, although other authors consider it as soft tissue tumor of uncertain type, as it lacks its precisely...
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defined, normal tissue counterpart. Low-grade fibromyxoid type, hyalinizing spindle cell tumor with giant rosettes, and SEF form so called fibrosing fibrosarcoma group. SEF is a rare and poorly recognized variant of fibrosarcoma originally described by Meis-Kindblom et al. in 1995. Tumor affects mainly young and middle aged adults, and presents as deep-seated mass on the limbs, limb girdles, trunk and neck. Most arise within the skeletal muscle, deep fascia or peristeme. Examples of primary involvement of neuraxis and bone have also been reported. Grossly, the tumor is gray-white, usually well circumscribed and lobulated with occasional examples showing cystic or myxoid change, measuring mostly 5-10 cm in greatest diameter. Histological hallmark of SEF are nests and cords of uniform and relatively small round to oval epitheloid cells, which usually have a clear cytoplasm, set in an extensive, hyalinized stroma. This histological growth pattern in the form of infiltrating epitheloid cells with prominent sclerosis is highly suggestive of a carcinoma. Foci with a more fascicular pattern of conventional fibrosarcoma, also with myxoid and even chondro-ossesous matrix are commonly present. The chromatin pattern of the nuclei is finely stippled to vesicular with eosinophilic nucleoli. Polymorphism is minimal and mitotic figures are usually scarce whereas some tumors may have a high mitotic rate with more than 5 mitoses per 10 hpf. Immunohistochemically all tumors stain strongly with vimentin, and up to one half cases show membranous immunoreactivity with epithelial membrane antigen. Neural markers including S-100 protein and NSE are positive in small number of cases. We have found a strong and diffuse vimentin staining in both cases, with weak and focal immunoreactivity with epithelial membrane antigen in the second case. Neural markers were negative in both cases. Ultrastructurally the tumor cells have the features of fibroblasts containing abundant rough endoplasmic reticulum, intermediate filaments and Golgi apparatus producing collagen secretory granules. Based on the previous reports, Eyden et al. proposed diagnostic criteria for this uncommon tumor: the presence of medium sized cells, clear or pale cytoplasm, cellular arrangement in cords and strands, a dense collagenous stroma and previously described immunohistochemical and ultrastructural findings. The differential diagnosis is wide and includes infiltrating carcinoma (particularly infiltrating lobular carcinoma of the breast), sclerosing lymphoma, synovial sarcoma, clear cell sarcoma of tendons and aponeuroses, epitheloid sarcoma, epitheloid leiomyosarcoma, extraskeletal myxoid chondrosarcoma, along with a variety of benign fibrous proliferations such as desmoid, hyalinizing fibroma, leiomyoma or fibromyxoma. In most instances use of the strict morphological criteria in the context of the clinical settings, followed by immunohistochemical analysis, and ultrastructural analysis in dubious cases, are helpful to confirm the proper diagnosis. The awareness of the existence of this rare entity will prevent eventual misdiagnosis of this neoplasm as a benign lesion, which may be followed by inadequate surgical excision and the high rate of local recurrences. Standard therapy is wide surgical excision with long-term follow-up. In spite of low-grade histology SEF has high local recurrence rate, and high metastatic potential, primarily in the lungs, several years after surgical removal. In the series by Meis-Kindblom et al., which comprised 25 cases, persistent disease or local recurrences were observed in 53%, and metastases in 43% of cases. In the series by Antonescu et al., which comprised 16 cases, recurrence rate was 50%, and distant metastases were observed in 86% of patients. Patients with tumors on the trunk, those with large tumors, and those of male gender may have a worse prognosis. These observations are in accordance with a clinical course of our first case who demonstrated multiple recurrences, with death of metastatic disease four years after diagnosis.

References