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CASE REPORT

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Epithelioid fibrosarcoma of the ovary

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Abstract Recently, low-grade fibromyxoid sarcoma/hyalinizing spindle cell tumor with giant rosettes (LGMFS/HSCT) and sclerosing epithelioid fibrosarcoma (SEFS) have come to be recognized as distinctive types of fibrosarcoma. Because their pathological features seem to sometimes overlap, it may be that these tumors belong to a similar entity. We report an aggressive sarcoma with unusual histology arising from the right ovary of a 44-year-old woman. The tumor was 12 cm in size, and there were multiple distant metastases to lung, kidney, stomach and bones. Microscopically, the tumor was composed of broad sheets or variously sized nodules of polygonal epithelioid cells accompanied by hyalinous stroma, resembling SEFS. The hyalinous nodules surrounded by the palisading epithelioid cells, as seen in a rosette of HSCT, were scattered. Between these nodules, spindle cells arranged in fascicles or whorled bundles, mimicking LGMFS, proliferated. Immunohistochemical and ultrastructural analyses revealed fibroblastic differentiation of epithelioid cells and the myofibroblastic nature of the spindle tumor cells. We think the present tumor is a distinctive epithelioid fibrosarcoma with the combined features of SEFS and LGFMS/HSCT, suggesting their intimate relationship.

Keywords Fibrosarcoma · Epithelioid · Rosette · Low-grade · Ovary

Introduction

In the past, fibrosarcoma was one of the most common soft tissue malignancies, but it became rare to encounter a convincing case of fibrosarcoma, since many spindle cell sarcomas are now classified into specific entities according to their clinicopathological, immunohistochemical and ultrastructural characteristics [11]. In contrast, recently some tumors have been described as being a distinctive type of fibroblastic sarcoma, which include low-grade fibromyxoid sarcoma (LGFMS) [2, 3, 6], sclerosing epithelioid fibrosarcoma (SEFS) [1, 4, 8] and hyalinizing spindle cell tumor with giant rosettes (HSCT) [5, 7, 9]. Each tumor has characteristic clinicopathological features, but it has been pointed out that sometimes (to varying degrees) they have common histological components, suggesting their intimate relationship [5, 10]. We report a case of distinctive epithelioid fibrosarcoma with multiple distant metastases arising from the ovary. Although it predominantly had the features of SEFS, they were frequently intermingled with distinctive histological features resembling those of LGFMS and HSCT. Its immunohistochemical and ultrastructural characteristics are also described.

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Clinical history

A 44-year-old woman was admitted to a gynecological hospital with a complaint of hypermenorrhea, and a uterine myoma-like pelvic tumor was found. She had been examined medically every year, and no abnormal changes were reported in her gynecological organs. The tumor grew rapidly for 3 months, and she was admitted to our hospital. Radiological examinations revealed an 11-cm pelvic tumor arising from her right ovary and multiple nodules, which appeared to be metastases in the lungs, left kidney and pelvic, femoral and vertebral bones. The pelvic lymph nodes were also involved. A small submucosal tumor was found by gastrointestinal endoscopy. Histological examinations of the kidney and stomach suggested SEFS. A simple hystero-oophorectomy was performed to make the diagnosis. Subsequently, she underwent irradiation of the rapidly growing bone metastases, and she survived for 4 months with disease. After the final pathological diagnosis, her whole body was re-examined, but no soft tissue or skin lesions were found. She had no previous history of tumor extirpation.

Materials and methods

Immunohistochemistry and electron microscopy

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections using the streptavidin-biotin-complex method (LSAB kit, Dako Japan, Kyoto, Japan). The primary antibodies and their final dilutions were: CD31 (1:25; Dako Japan), CD34 (NU-4A1, 1:100; Nichirei, Tokyo, Japan), CD57 (1:100; Becton Dickinson, CA, U.S.A.), high molecular weight caldesmon (h-CD, 1:50; Dako Japan), c-kit (polyclonal, 1:50; IBL, Gunma, Japan), cytokeratin (AE1/AE3, 1:50; Dako, Japan and CAM5.2, prediluted; Becton Dickinson), desmin (D33, 1:50; Dako), epithelial membrane antigen (EMA, E29, 1:50; Dako), neuron-specific enolase (polyclonal prediluted; Nichirei), α-smooth-muscle actin (1A4, 1:100; Dako), S-100 protein (polyclonal, 1:1,000; Dako) and vimentin (V9, 1:25; Dako). For electron microscopy, fresh tumor tissue was fixed in 2% glutaraldehyde and osmium tetroxide, processed into epoxy resin using conventional methods and examined with a JEM-1200EX transmission electron microscope (JOEL Ltd., Tokyo, Japan).

Results

Gross and microscopic findings

The right ovarian tumor had a 12.0-cm maximum diameter and was firm, well demarcated and tan-gray in color. Some cystic degenerative areas with hemorrhage were observed in the central area of the tumor. No macroscopic necrosis was present.

Microscopically, the tumor was composed of broad sheets or variously sized nodules of epithelioid cells, which were separated by various amounts of hypocellular and myxoid spindle cell area (Fig. 1). The epithelioid cells with polygonal clear or eosinophilic cytoplasm and round or ovoid vesicular nuclei, sometimes with prominent nucleoli, were arranged in cords and small nests in the fibrous and hyalinous stroma (Fig. 2). Although mild to moderate nuclear atypia was common, prominent atypia, cellular pleomorphism or multinucleated giant cells were not seen. Mitoses were present but not numerous. The tumor nodules were often accompanied by one or a few thin-walled venules. In addition, tumor cells occasionally palisaded in the periphery of the nodules and surrounded the hyalinous cores, resembling rosettes (Fig. 3). Epithelioid tumor cells in the periphery of the nodules were often degenerated and necrotic. Spindle tumor cells had eosinophilic fibrillary cytoplasm and were arranged in vague fascicles or whorls with myxoid stroma. They had uniform oval nuclei, and atypia was minimal. Coagulation necrosis of the tumor was seen focally.

Biopsy specimens of metastatic lesions of the stomach and kidney showed small nodules composed of epithelioid tumor cells in the hyalinous stroma similar to the primary site. Rosette-like structures were not found.

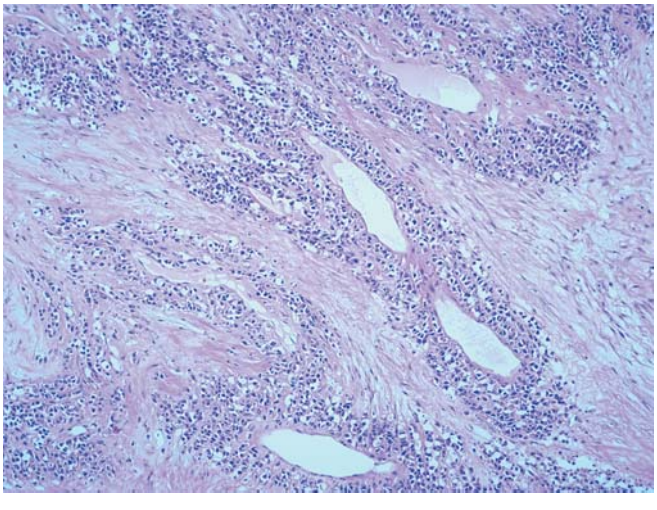

Fig. 1 Epithelioid nodules and hypocellular myxoid spindle cell area were intimately intermingled. Nodules were often accompanied by a central blood vessel

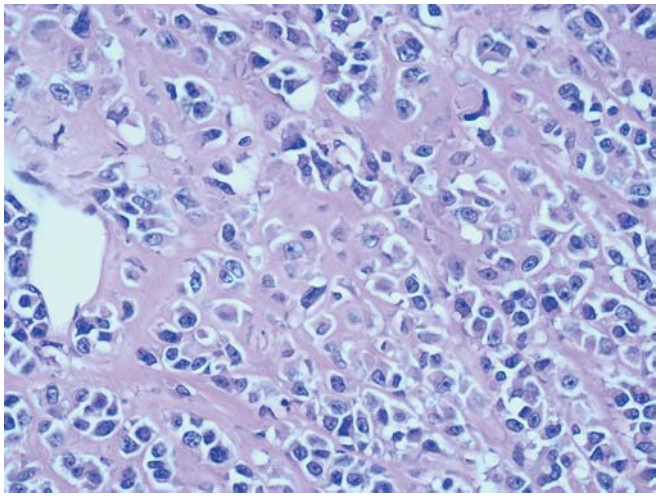

Fig. 2 Epithelioid tumor cells in the fibrous or hyalinous stroma

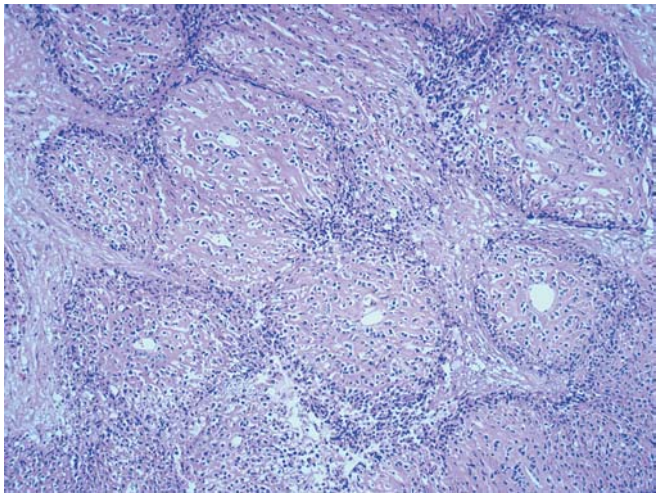

Fig. 3 Accumulation of many rosette-like hyalinous nodules. The tumor cells in the periphery of nodules often degenerated and tended to become necrotic

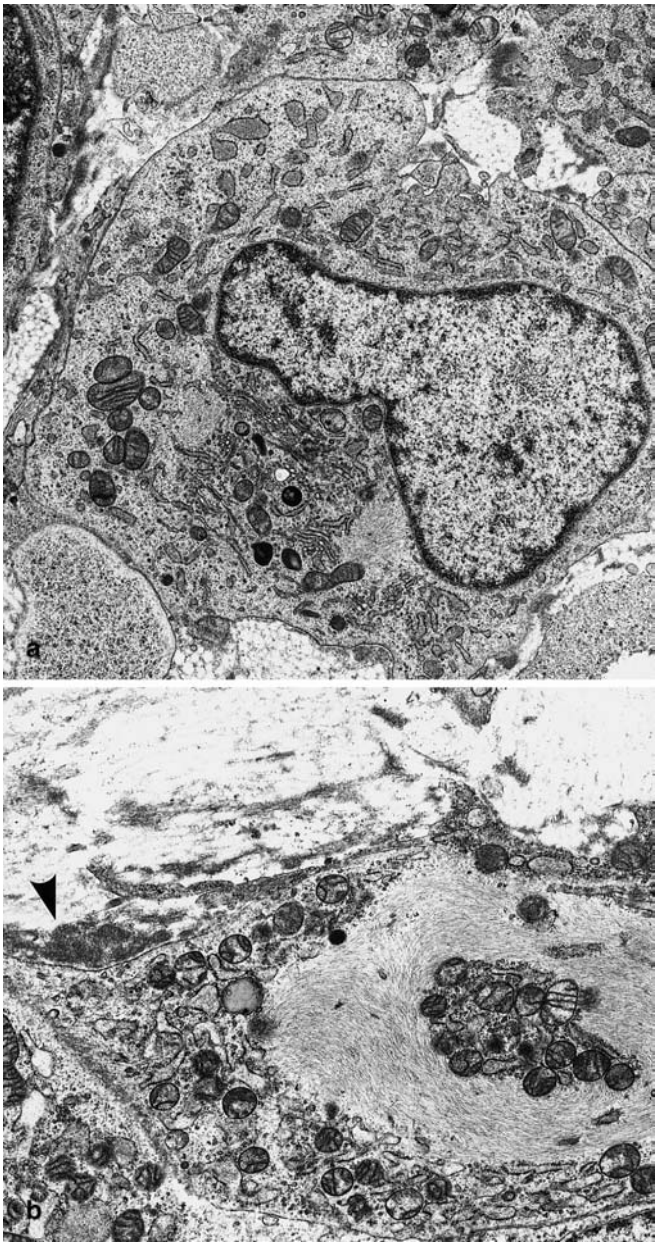

Fig. 4 The epithelioid tumor cell had much rough endoplasmic reticulum, numerous mitochondria and Golgi apparatus in the cytoplasm, ×6500 (**A**). A large number of vimentin-type intermediate filaments adjacent to the nucleus were also a common feature. External lamina-like material surrounded the epithelioid tumor cells (*arrowheads*), ×12,000 (**B**)

Immunohistochemistry

The tumor cells were positive for vimentin diffusely and neuron-specific enolase focally but were completely negative for cytokeratin (CAM5.2) and EMA. Although scattered epithelioid tumor cells were positive for keratin (AE1/AE3), the reactivities were often restricted to the perinuclear cytoplasm. Spindle cells were diffusely positive for α-smooth-muscle actin. The tumor cells were negative with all other antibodies.

Ultrastructure

The epithelioid cells had abundant and often dilated rough endoplasmic reticulum, numerous mitochondria and Golgi apparatus in their cytoplasm (Fig. 4A). A large number of intermediate filaments adjacent to the nuclei were also a common feature (Fig. 4B). Although epithelioid cells were intimately adjoined each other, no intercellular junctions were seen. Occasionally, external lamina-like material surrounded the epithelioid tumor cells. Spindle cells exhibited a distinct myofibroblastic differentiation, such as abundant actin filament with focal density, rough endoplasmic reticulum and well-developed fibronexus junctions. A few stellate fibroblastic cells surrounded by external lamina-like material were scattered around the nest of epithelioid cells.

Discussion

Since epithelioid fibrosarcoma has not been reported in the ovary and other internal organs [1, 4, 8], the differentiation from primary and metastatic carcinoma using light microscopy was problematic. Indeed, if epithelioid fibrosarcoma occurs in the internal organs, it would be easily misinterpreted as undifferentiated carcinoma unless immunohistochemical and ultrastructural analyses are performed. The epithelioid cells of the present tumor were immunohistochemically negative for epithelial markers, including cytokeratin (CAM5.2) and EMA, except for focal positivity of cytokeratin (AE1/AE3). Ultrastructural examination revealed a well-developed rough endoplasmic reticulum, absence of typical external lamina, lack of intercellular junctions and abundant vimentin-type intermediate filaments. These findings indicated fibroblastic differentiation of epithelioid tumor cells, and a diagnosis of fibrosarcoma was considered. The whole body radiological examinations failed to find a soft tissue mass, which is likely the primary lesion. In addition, the patient had no history of tumor extirpation. Thus, we think the present tumor is of ovarian origin.

Histologically, the present tumor showed a distinctive complex feature composed of a broad or nodular epithelioid cell component with sclerosing stroma, a hypocellular fibrous and myxoid area and many rosette-like lobules often accompanied by central vessels. These histological features resembled not only SEFS but also LGFMS or HSCT. SEFS was first reported by Meis-Kindblom et al. [8] as a variant of fibrosarcoma with relatively low-grade malignant potential and with characteristic epithelioid cells and strikingly hyalinized stroma. LGFMS and HSCT were first reported by Evans [2] in 1987 and by Lane et al. [7] in 1997, respectively, but they are now understood to be a single tumor entity of distinctive low-grade fibrosarcoma with or without characteristic rosettes [5, 7, 10]. In contrast, it has not been elucidated whether SEFS and LGFMS/HSCT belong to an analogous entity. Age and the primary site of SEFS and LGFMS/HSCT are almost identical, both tumors af-

fecting the deep soft tissues of young to middle-aged adults [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The prognosis of SEFS was considered to be rather favorable at first [8], but a recent study by Antonescu et al. [1] demonstrated its high metastatic potential (86%) and mortality (57%) in contrast with the indolent low metastatic rate of LGFMS/HSCT [5]. Their light microscopy features seem to overlap occasionally, and SEFS-like areas can be found in LGFMS/HSCT [5, 10]. Additionally, hypocellular fibrous areas resembling fibroma or LGFMS have been described in SEFS [1], whereas giant rosettes characteristic of HSCT have not been reported to our knowledge. We believe the present tumor is a distinctive case, suggesting an intimate relationship between SEFS and LGFMS/HSCT. In the present case, rosette-like structures were composed of atypical epithelioid cells identical to the tumor cells in the SEFS area and often included central small vessels. A similar feature was described by Reid et al. [10] as an unusual HSCT. The biological nature of the present tumor appears to be closely related to that of SEFS rather than to LGFMS/HSCT because of its aggressive behavior with multiple distant metastases and the atypical feature of epithelioid cells.

Although spindle tumor cells of LGFMS have been reported to sometimes be positive for α-smooth-muscle actin, suggesting myofibroblasts [6], ultrastructural myofibroblastic differentiation has not been reported in the previous studies on LGFMS [6, 9, 12]. The present case study demonstrates well-developed thin actin filaments with focal densities and fibronexus junctions characteristic of myofibroblasts in the spindle tumor cells. This finding seems to be well correlated with intensive expression of α-smooth-muscle actin in spindle tumor cells. In addition, external lamina-like amorphous material surrounding epithelioid and fibroblastic stellate cells was frequently seen. Similar material was found in the previous cases of both SEFS and HSCT [1, 9]. Its meaning has been unclear, but it may be an ultrastructural characteristic, since usual fibrosarcomas do not include such material.

Epithelioid fibrosarcoma of the ovary should be differentiated from primary and secondary epithelioid tumors. Among these, distinguishing it from undifferentiated carcinoma is most difficult, and it seems impossible to differentiate on the basis of cellular morphology alone. Characteristic sclerosing collagenous stroma surrounding tumor cell is an important feature for differentiating the present tumor from carcinoma. Immunohistochemical examination using several epithelial markers is necessary for final diagnosis, but it should be remembered that epithelioid fibrosarcoma can exhibit focal immunoreactivity for epithelial markers, especially for EMA [1]. Because of its variable epithelioid feature, synovial sarcoma is included in the differential diagnosis. Although synovial sarcoma may have an extensive hyalinous stroma, a conventional epithelioid or spindle cell area is invariably intermingled. Finally, because the sclerosing stroma sometimes mimics an immature osteoid, epithelioid fibrosarcoma may be confused with osteosarcoma, including small cell type. However, osteosarcoma contains more matured osteoid or bone, at least focally, and malignant cartilaginous tissue frequently.

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