Case Reports

Beata Maksymiuk[1], Anna Smok-Ragankiewicz[1], Mirosław Śnietura[1], Dariusz Lange[1], Grzegorz Słomian[2]

Diagnostic Problems Concerning Epithelioid Sarcoma – Case Analysis

[1]Department of Tumor Pathology, Center of Oncology, Maria Skłodowska-Curie Memorial Institute, Gliwice Branch,
[2]Department of Chemiotherapy, Center of Oncology, Maria Skłodowska-Curie Memorial Institute, Gliwice Branch

We discuss here five cases of epithelioid sarcoma (ES) with final diagnosis established after reexamination of initial findings. Problems with differential diagnosis of these neoplasms arise since their microscopic picture may simulate several other pathological conditions such as non-neoplastic granulomatous reactions, squamous cell carcinomas and adenocarcinomas, melanomas and soft tissue sarcomas with epithelioid component. Final ES diagnosis requires presence of cytokeratin, EMA and vimentin in neoplastic cells, as confirmed by immunohistochemical reactions. Differential diagnosis is also helped by concurrent cytology assessment that allows recognizing more easily such characteristic features as presence of plasmacytoid or spindle-shaped cells.

Introduction

Epithelioid sarcoma (ES) is a rare soft tissue sarcoma described for the first time in 1961 by Laskowski as a lesion originating from fascial structures [15]. At the time this report did not encounter wider reaction and no new disease entity was established. In 1968 Bliss et al. described four similar cases [3] but widespread recognition of this entity in diagnostic histopathology ensued only after a report from Enzinger [7]. Nowadays ES is classified as a neoplasm with well-recognizable microscopic and ultrastructural features but its histogenesis continues to be elusive. Diagnosis may be sometimes quite problematic since lesion texture can resemble both benign and malignant neoplasms.

Epithelioid sarcoma occurs predominantly in young adults in distal parts of extremities, especially on fingers, palms, feet and forearms. Less frequently it occurs on thighs, lower legs, buttocks [8, 11] and in the chest wall [1]. Substantially rarer is its atypical localization, for example penile, lingual or vulval [22]. In ca. 20% of cases lesions are preceded by trauma [11]. Typical clinical picture features shallow-localized single or multiple plano-convex often ulcerated skin nodules; occasionally ES appears as subcutaneous nodules covered with normal skin and infiltrates surrounding tissues [8, 11, 20]. Usually, no invasion of epidermis is diagnosed [8]. Less frequently ES is located deeper; it is then associated with fasciae or aponeuroses and reaches greater size. In some cases ES develops slowly but gives local recurrences and, distinct from other sarcomas, leads to metastases into lymph nodes [8, 11]. A characteristic ES feature is the formation of satellite nodules and spread along fasciae and vasoneural structures; as a result ES cells can sometimes be found as far as 30 cm away from the primary lesion [8]. This is the main source of difficulties encountered in radical treatment of the lesion. Prognostic factors include location and size of the lesion, mitotic index value and presence of vascular invasion [8, 11]. So far, there is no effective chemotherapeutic treatment for ES since this neoplasm shows multidrug resistance [14]. Morphologically, ES exhibits heterogenous variant forms; besides classical (distal) ones several rarer histological variants can occur. Among them are "fibroma-like", angiomatoid and proximal forms [8–12, 16, 17, 20].

Case Descriptions

Material and Methods

We demonstrate here a few cases of epithelioid sarcoma with particular emphasis placed upon difficulties encountered during differential diagnosis. The slides and paraffin blocks were received in aim to consult them in the Department of Tumor Pathology, Center of Oncology, Maria Skłodowska-Curie Memorial Institute, Gliwice Branch. Comparison of clinical-morphological features is shown in Table 1.

TABLE 1
Clinicopathological features of patients with epithelioid sarcoma diagnosis

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Male	Male	Female	Male
Age	20	41	52	65	41
Duration of illness	4 months	18 months	6 months	5 months	6 years
Localization	Right arm	Buttock	Right forearm	Chest	Right inguinal region
Tumor dimensions	2.0 ×1.2cm	No data	8.0 ×7.0 cm	15.0 × 6.0cm	6.7 × 2.8 cm
Diagnosis after FNA	Sarcoma susp.	Sarcoma susp.	Sarcoma susp.	Not done	Not done
Initial histopathologic diagnosis	Anaplastic carcinoma	Adnexoidal carcinoma	Sarcoma	Carcinosarcoma	Squamous cell carcinoma
Metastases	Lymph nodes, skin	Lungs	Lungs	Not known	Lungs, skin, vertebrae
Follow up	Died	Alive	Died	Not known	Alive

Case 1. A 20-year old woman with a blue-violet 2.0 × 1.2 cm painless nodule present on the right arm for four months. Initial diagnosis suggested anaplastic adnexal skin carcinoma with lymphoma to be considered in differential diagnosis (167539–540). Within three weeks from surgery a recurrence reaching shoulder joint appeared (10.0 × 4.5 cm) that presented in right armpit a lymph node conglomerate mass of 6 cm in diameter. Microscopic examination of biopsy material from FNA revealed cytological features of nonepithelial malignancy (221425). Histopathological examination of post-operative material (200321) together with immunohistochemistry (2946) and reexamination of initial histopathology slides allowed diagnosing epithelioid sarcoma. The amputation and subsequent chemiotherapy was performed but within subsequent 3 months this neoplasm infiltrated and ulcerated both skin and subcutaneous chest tissues, infiltrated pectoral muscles, gave metastases to jugular and supraclavicular lymph nodes as well as to contralateral axillary lymph nodes.

Case 2. A 41-year old male with subcutaneous painful tumor mass in the gluteal area present for 18 months. Initial histopathological diagnosis revealed probable adnexal skin cancer (4403–4). The recurrence of the tumor (200357) was located subfascially and caused infiltration of rectal sphincters. The patient received radiotherapy and several courses of chemiotherapy but the dissemination into the lungs occured.

Case 3. A 52-year old male complaining of pain in his right forearm lasting six months. CT scan revealed a 5.0 × 4.0 cm infiltration in the region of interosseous membrane with degradation of cortex layer in both forearm bones. FNA biopsy suggested sarcoma-like infiltration (2040). Histopathological examination of the lesion specimen together with immunohistochemistry allowed diagnosing epithelioid sarcoma (199344). This diagnosis was confirmed by examination of post-operative material (199772–3). The amputation was performed and one year after the tumor resection the metastases into the lungs occurred and the patient died shortly after that.

Case 4. A 65-year old woman complaining of pain in right subscapular area and lasting five months. CT scan revealed a skin-reaching pathological tissue mass of the size 10.0 × 7.0 cm in postero-lateral part of right pleural cavity, closely bound to thoracic cage wall and stretching to Th6-Th7 vertebral body, with concomitant osteolysis of posterior costal segments and infiltration of costal muscles. Intrasurgery findings suggested diagnosis of malignant non-epithelial neoplasm probably malignant schwannoma (84933). Following immunohistochemical study (2124) sarcomatoid carcinoma was determined. Final diagnosis was established after consulting examination (13933) and after another round of immunohistochemical panel study (9221). Due to the advancement of the disease the patient was qualified for paliative radiotherapy.

Case 5. A 41-year old man with left inguinal tumor presenting for six years was diagnosed because of pain and left lower leg oedema. This tumor was presented as hypoechogenic area, which consequently increased in size up to the 6.7 × 2.8 cm with formation of the skin fistula. The biopsy taken initially from the tumor revealed nodular fibrosis, the next one was diagnosed as cancer metastasis, probably squamous cell carcinoma (7240), which was subsequently diagnosed as epithelioid sarcoma (9998). The dissemination occurred and the metastases to the lungs and vertebrae and skin were recognized.

In order to establish final histopathological diagnosis, a panel of immunohistochemical assays based on ABComplex method was performed in each case. The sections 4 μm-thick were made from each paraffin block routinely obtained following fixation in 10% formalin, mounted on slides and then deparaffinized and hydrated through a series of xylenes and alcohols. The following murine monoclonal antibodies (DAKO) were used: anti-human cytokeratin (M0821); anti-human epithelial membrane antigen (M0613); anti-vimentin (M7020); anti-human CD34 Class II (M7165); anti-human muscle actin (M0635); anti-human melanosome (M0634); anti-human desmin (H7094); anti-human cytokeratin 5/6 (M7237); anti-human mesothelial cells (M3505) and rabbit anti-cow S-100 (Z0311).

Light microscopy appearance

Histopathology specimens revealed proliferation of acidophilic epithelioid and spindle-shaped cells showing variably intense pleomorphism and possessing distinct nucleoli. Usually, transitory stages of one cell type into another could be seen. Focally, the arrangement of cells around necrotic areas suggested granuloma-like structures. Features of perineural proliferation of neoplastic cells, geographic necrosis and as in case 4 the fields of osseous metaplasia were also visible. In case 1 the rhabdoid features were also seen. All analyzed cases were recognized as proximal-type ES. In each case, depending on the histological picture obtained, the result of immunohistochemical panel assays performed in paraffin sections was analyzed. The results important for the diagnosis are demonstrated in Table 2.

Cytological smears of the material from FNA biopsies revealed mainly scattered polygonal, or less frequently, spindle-shaped cells with abundant acidophlic and sometimes granular cytoplasm, sometimes with large intracytoplasmic vacuoles. Groups of cells, loose sheets and syncytial forms were scarce. The cellular pleomorphism

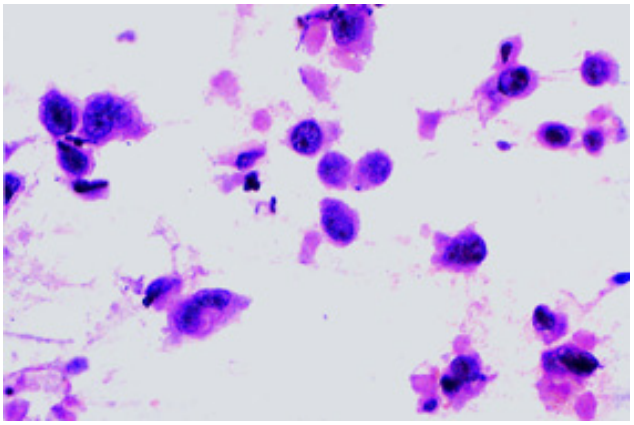

Fig. 2. Cytologic picture of epithelioid sarcoma – case 2. HE. Magn. 200×.

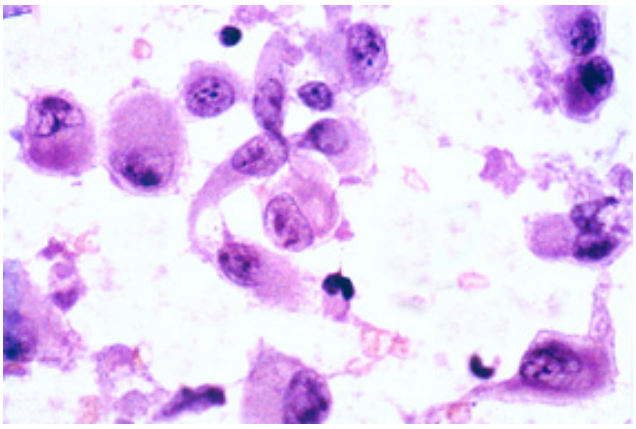

Fig. 1. Cytologic picture of epithelioid sarcoma – case 1. HE. Magn. 400×.

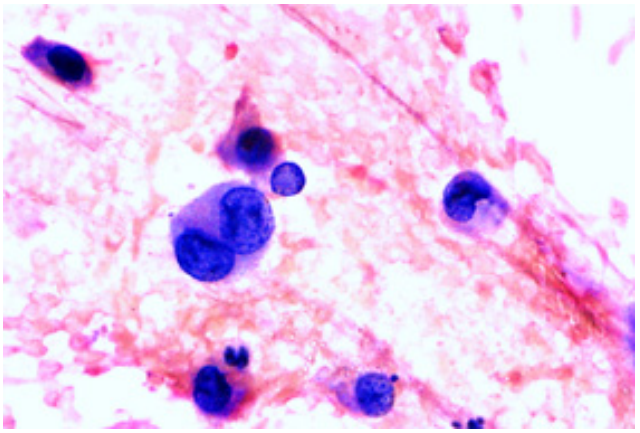

Fig. 3. Binucleated cell in epithelioid sarcoma – case 3. HE. Magn. 400×.

TABLE 2
Immunohistochemical diagnosis – results

	Case 1	Case 2	Case 3	Case 4	Case 5
EMA	positive	positive	positive	positive	positive
Cytokeratin	positive	positive	positive	positive	positive
Vimentin	positive	positive	positive	positive	positive
S-100 protein	negative	focal positivity	negative	negative	positive
CD 34 antigen	negative	negative	negative	negative	negative

was visible, round or oval cell nuclei were rather large, centrally located or displaced towards periphery, with finely granular, vesicular or evenly distributed chromatin; coarse-grained chromatin was also occasionally visible (Figs. 1 and 2). Cell membrane was smooth or irregular, nucleoli rather large and distinct, either round or irregular. Very rarely bi- or polynucleate cells could be seen (Fig. 3). Rather numerous mitotic figures were visible.

Discussion

The histogenesis of ES remains unclear [20]. ES exhibits features of epithelial differentiation and therefore could be regarded as a form of carcinoma of soft tissue [16, 20]. The microscopic picture of typical epithelioid sarcoma variants reveals proliferating epithelioid or spindle-shaped cells, sometimes in palisade arrangement around a central necrotic area, as was seen in our cases, sometimes forming single or merging nodules that resemble granulomas. Epithelioid cells have strongly acidophilic or glassy cytoplasm while in spindle-shaped ones the cytoplasm is acidophilic or clear [8, 10, 20, 21, 24]. The collagen fiber-rich subtype that resembles fibroma or fibrohistocytoma forms a variant called "fibroma-like". This variant is dominated by proliferation of spindle-shaped cells that show moderate atypia. The so-called angiomatoid variant is characterized by cystic degeneration and by heavy bleedings from the lesion [13]. Compact type growth with the presence of large rhabdoid neoplastic cells is typical for giant-cell or rhabdoid variant [6, 8, 9, 12, 16]. This type of growth we have seen in cases 1 and 4. Since ES cells are undifferentiated myofibroblasts with primitive epithelial features, they can occasionally differentiate in other directions, for example towards osteoid or chondral types or possess intracytoplasmic vacuoles imitating lumen of blood vessels [4]. Smith and al. have shown that ES cells lack tangible immunohistochemical reaction for the presence of E-cadherin. This suggests that, in at least some cases, epithelial differentiation in ES is not complete [23]. It is not clear whether the epithelial features present in ES derive from metaplasia of mesenchymal elements [20]. It can be also possible that ES is a peculiar form of epithelioid hemangioendothelioma [20].

The so-called proximal variant presents a special ES form necessitating differentiation from extrarenal rhabdoid tumor. It reveals large vesicular nuclei and the so-called rhabdoid hyaline inclusions in the cytoplasm. These inclusions are deposits of intermediate filaments localized near nuclei [5, 6, 12, 13]. Proximal type of ES is characterized by a proximal location, deep invasion and necrosis. Sometimes the rhabdoid features are prominent. This form is associated with more aggresive clinical course. In our presentation three persons died because of the disease progression.

Recognizing ES is sometimes substantially difficult since differential diagnosis should exclude several other disease processes including granulomatous reactions (inflammatory and annular granulomas), fibromatoses, squamous cell carcinomas, adnexal skin carcinomas, synovial sarcoma, malignant fibrous histiocytoma, leiomyosarcoma, myxoid chondrosarcoma, malignant peripheral nerve sheath tumor, melanomas, malignant epithelioid hemangioendotheliomas and extrarenal rhabdoid tumors [6, 7, 10, 17, 18, 24]. Especially when atypical clinical data are present or in diagnostically dubious situations immunohistochemical study with a correctly chosen antibody panel plays a substantial role. Cytological picture may also prove very helpful [4].

Epithelioid sarcoma differs from granulomatous reaction by a greater degree of cytological atypia and by the presence of mitotic activity. This is particularly easy to determine in cytological preparations that clearly differ in morphologies of epithelioid histiocytes and ES cells. Multinucleate ES cells are rarely seen; such cells are more numerous in granulomatous reaction. Neoplastic cells in ES show immunoreactivity to cytokeratins and EMA, whereas in granulomas these reactions are negative.

Squamous cell and adnexal skin cancers are infrequent among patients belonging to the typical age and location ES group. Squamous cell carcinoma metastases show occasionally keratinization features which are absent in ES. On the other hand, strong expression of both cytokeratins and EMA is common for these neoplasms.

CD34 antigen is present in only half of ES cases [2]; but in our material in no case this reaction was so satisfactory to recognize it as positive. In squamous cell carcinomas presence of CD34 antigen is exceptional. Adnexal skin carcinomas can show features of myoepithelial differentiation while in adjacent glands dysplasia may be seen; these in turn cannot be determined in epithelioid sarcoma.

Epithelioid and spindle-shaped ES cells can resemble melanoma. The latter is, however, strongly positive for S-100 protein presence, and in majority of cases also HMB-45-positive. No HMB-45-positive ES case has been reported so far. Immunohistochemical diagnosis is mandatory in such case since cytology and histopathology pictures may not differ much especially if the S-100 positivity in ES is observed.

In about 30% of ES cases cells with intracytoplasmic vacuoles are seen that require differentiation from malignant epithelioid tumor of vascular origin (such as epithelioid hemangioendothelioma and epithelioid angiosarcoma) [8]. Differential immunohistochemical diagnosis should take under consideration in such case also factor VIII and CD31

antigen. Additionally, cytokeratin expression, while frequent in ES, is practically absent from epithelioid vascular tumors [8].

Rhabdomyosarcoma can present elongated cells with granular acidophilic cytoplasm; the immunohistochemical reaction for the presence of muscle markers and positive PAS reaction allows, however, to differentiate it from ES.

Epithelioid sarcoma has several features common with the so-called "*soft tissue rhabdoid tumor*". In these cases a multinodule type of growth and positive CD34 antigen reaction favor rather ES diagnosis. In some cases though it may be impossible to differentiate these neoplasms due to rhabdoid appearance of cells. It is especially common in proximal-type SE. This form is connected with a more aggressive clinical course as we have seen in case 1.

Prior to establishing ES as a separate entity it had been diagnosed in a variety of ways. Due to granuloma-like appearance it was rated among granulomatous inflammations [7]; due to epithelium-like fields it was wrongly qualified as carcinoma, synovial sarcoma or as melanoma [8, 9]. The advent of routine immunohistochemical diagnostics corroborated particular problems of differentiating these lesions from carcinomas. Coexpression of cytokeratin and epithelial membrane antigen is seen in majority of carcinomas; coexpression of cytokeratin and vimentin in epithelioid tumors requires for differential diagnosis of ES to take into consideration kidney, lung, stomach, uterus, ovary and thyroid carcinomas. Although such coexpresion is typical in ES, very rarely there may occur cases that are vimentin-negative [2] and cytokeratin-negative [2, 17]. Thus, immunomorphological features exemplify a very substantial potential source of diagnostic mistakes since immunoreactivity towards cytokeratin and EMA is a permanent feature of these neoplasms, like in carcinomas.

Lack of clinical picture knowledge together with inadequate knowledge of disease entities and/or incorrectly chosen immunohistochemical assay panel may all lead to incorrect diagnoses excluding ES. Performing simultaneously an FNA biopsy from suspected lesions seems especially helpful. In cytological smears in particular, ES reveals its non-epithelial features despite the presence of epithelial-like fields in histology preparations. Such fields may be wrongly interpreted as carcinoma texture or even granuloma lesions.

Knowledge of clinical picture seems particularly important. The occurrence of anaplastic adnexial skin carcinoma in young adults is exceptionally rare. More frequently it is undiagnosed epithelioid sarcoma. On the other hand, one should always preclude in adult individuals the presence of carcinoma texture or carcinoma metastasis in atypical localization. Literature data and our own observations suggest performing, in case of a suspected ES lesion, a fine needle aspiration biopsy or cytological imprint from freshly collected material together with immunohistochemical assay panel. The latter should routinely include cytokeratin, vimentin and epithelial membrane antigen. We were not able to prove the CD34 antigen immunoreactivity in our material, but some authors use it in the differential diagnosis.

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Address for correspondence and reprint requests to:
Beata Maksymiuk
Department of Tumor Pathology
Center of Oncology
Maria Skłodowska-Curie Memorial Institute, Gliwice Branch.
Wybrzeże Armii Krajowej 15, 44-100 Gliwice
Phone: 0 32 2789410
Fax: 0 32 2789415
E-mail: fibros@poczta.wp.pl