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Poorly differentiated angiosarcoma without vasoformative channels but with focal intracytoplastic vacuoles mimicking liposarcomas☆

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Abstract Angiosarcoma (AS) showed diverse morphologies from well formed malignant vasculatures to poorly differentiated tumor with only a few clues of endothelial differentiation. Herein reported are two cases of AS without primitive vasoformative channels (VC). They showed, instead, a very few foci of intracytoplasmic vacuoles (ICV) that mimicked liposarcoma. The two cases were found in 12 cases of AS in computer database. Both are men, 57 and 68 years. One is cutaneous (foot) AS and another is soft tissue (thigh) AS. The largest diameter of cutaneous AS was 5 cm, and that of soft tissue AS 9 cm. The prognosis of both patients was poor; both died of metastases 4 and 6 years after initial presentation. In both cases, hematoxylin and eosin (HE) diagnosis was difficult because there were no VC, and most of the tumors were composed of primitive mesenchymal tissues. In both cases, however, a few very tiny foci consisting of ICV were seen. At first, the author considered them as mucins or fat, and suspected liposarcoma. In fact, they were pseudolipoblasts. Several mucin stains showed no mucins, and fat stains of frozen sections of formalin fixed tissue were negative for fat. Immunohistochemically, the vacuoles were positive for factor VIII-related antigen (F-VIII-RA), Ulex lectin, CD31, CD34, vimentin, p53 and Ki-67 (labeling index = 64% and 75%), but negative for various types of cytokeratins (CK), EMA, CEA, CA19-9, CD45, smooth muscle actins, S100 protein, myoglobin, HMB-45, Melan A, NCAM, and NSE. F-VIII-RA is specific and Ulex lectin and CD31 are relatively specific for endothelium. Therefore, the pathological diagnosis of AS could be made by the combined histologic features (ICV) and Immunohistochemical positivity of F-VIII-RA, Ulex lectin, and CD31. Thus, it appeared that the ICV may be the only clue of poorly differentiated or undifferentiated AS. In such undifferentiated cases, combined observations of meticulous histologic observations (intracytoplasmic lumens and ICV) immunohistochemistry of F-VIII-RA, Ulex lectin, and CD31 may be helpful in the diagnosis of poorly differentiated and undifferentiated AS. Electron microscopic observations were not done in the present study.

1. Introduction

According to WHO blue book of skin, cutaneous angiosarcoma (AS) is defined as a malignant neoplasm of endothelial cells [1]. Almost all cutaneous ASs are aggressive tumors, and emerge in one of the following settings: the head

Abbreviations: AS, angiosarcoma; ICL, intracytoplasmic lumen; ICV, intracytoplasmic vacuole; TEM, transmission electron microscopy; CK, cytokeratin.

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and neck tumors of predominantly male elderly patients (the most common setting) [2], tumors of the patients who have undergone mastectomy for breast cancer (Stewart–Treves syndrome) [3], lymphedema (congenital and acquired), or post irradiation [4]. Although AS can occur in any location of skin, the most common sites are scalp and head and neck regions [1–12]. The outcome is very poor [1–12].

According to the WHO blue book of soft tissue [13], soft tissue AS is defined as a malignant tumor the cells of which variably recapitulate the morphologic and functional features of normal endothelium. AS of soft tissue is a rare sarcoma, and its incidence is very low compared to cutaneous AS. The soft tissue AS usually affects old age persons with a peak of 7th decade. Most common sites of soft tissue AS are deep muscles of the lower extremities followed in order by arm, trunk, and head and neck region [13–15]. A significant proportion arises in the abdominal cavity. Like cutaneous AS, soft tissue AS is an aggressive tumor and the prognosis is not good.

In general, ASs of any locations show diverse morphologies, ranging from ASs with simple vasoformative channels (VC) to poorly differentiated ASs, in which the endothelial nature is seen in only a few areas without VC [1–15]. In the present study, the author selected this poorly differentiated AS from the author's computer files of the last 20 years.

2. Case report

The author reviewed the author's computed data files of AS in the last 20 years. There were 12 cases of AS; nine were cutaneous AS and three were soft tissue AS. The author reviewed them and found that of the 12 cases 10 cases showed VC and the diagnosis is relatively easy. In the remaining two cases, no VC were seen and diagnosis was difficult. The present study describes these two cases.

Both cases were men, 57 years and 68 years. One was cutaneous (foot) AS and another is soft tissue (thigh) AS. The largest diameter of the cutaneous AS was 5 cm, and that of soft tissue was 9 cm. The prognoses of both patients were poor; both died of metastases 4 and 6 years respectively after the initial presentation.

In both cases, hematoxylin and eosin (HE) diagnosis was difficult because there were no primitive VC, and most of the tumors were composed of primitive mesenchymal tissues (Fig. 1A–D). In both cases, few very tiny foci consisting of intracytoplasmic vacuoles (ICV) were seen in only a few areas (Fig. 1A–D). At first, the author considered them as mucins or fat, and suspected liposarcoma in both cases. In fact, pseudolipoblasts were seen, and the tumors were closely similar to liposarcoma (Fig. 1B and D).

A mucin histochemical study was done as previously reported. The employed techniques were mucicarmine, colloidal iron, periodic acid–Schiff (PAS), diastase-digestion PAS (d-PAS), alcian blue (AB) at pH 2.5 and at pH 1.0, and combined techniques of d-PAS/AB [20,21]. Several mucin stainings showed no mucins. Fat stains (Sudan Black and Oil red O) of frozen sections of formalin-fixed tissue were negative for fat in the tumor cells.

An immunohistochemical study was performed with the use of Dako Envision method (Dako Corp, Glostrup, Denmark), as described previously [16–19]. Immunohistochemically, the vacuoles were positive for factor VIII-related antigen (F-VIII-RA) (Fig. 2A), vimentin, Ulex europaeus agglutinin I, CD31 (Fig. 2B), CD34 (Fig. 2C), p53, and Ki-67 (labeling index =64% and 75%) in both cases. The ICV were clearly positive for F-VIII-RA, Ulex lectin, CD31, and CD34. They were negative for various types of cytokeratins (CK) including CKAE1/3, CAM5.2, CK7, CK8, CK18, CK19, CK20, EMA, CEA, CA19-9, CD45, smooth muscle actins, S100 protein, myoglobin, HMB-45 (melanosome), Melan A, NCAM, and NSE.

The diagnosis of AS was made by the combination observations of histology (ICV) and immunostainings (F-VIII-RA, CD31, Ulex lectin and CD34) in the absence of VC. Electron microscopic examination (EM) was not carried out because apparatus of EM was not available in the author's laboratory.

3. Discussion

The histological features of AS show a wide range of variations; in one extreme AS is composed of simple vascular malignant endothelium with numerous VC formations and in another extreme AS is so poorly differentiated that the endothelial natures are seen in only a few areas. The present 2 cases are the latter extreme. The author selected these 2 cases out of the 12 cases of AS, which were composed of 6 well differentiated ASs with numerous VC, 4 moderately differentiated ASs with a few VC formation, and 2 poorly differentiated ASs without VC. The diagnosis of AS is to find the nature of endothelium of the given tumors. The most apparent features of endothelium are VC composed of malignant endothelial cells on HE preparations. However, it was found in the present study that 2 of the 12 cases which the author experienced had no VC. Thus, these 2 cases were difficult to diagnosis.

The earliest features of vasoformation of endothelial cells are intracytoplasmic lumen (ICL) and ICV. However, these are common features of many cells such as glandular epithelium and vascular endothelium during their development, carcinogenesis and ontogenesis. They are seen in many cancers that recapitulate their embryonic ontogenesis. These ICL and ICV features are frequently seen in numerous malignancies in clinical cytology. Thus, ICL and ICV are not specific of AS, but the only clue of AS without VC.

In the present 2 cases, AS was very poorly differentiated and was composed largely of embryonic mesenchymal cells. No VC were seen. There were very small numbers of cells of ICV in the present cases. At first, the author considered that they are mucins (adenocarcinoma) or immature lipocytes