Cutaneous granular cell angiosarcoma

The majority of cutaneous angiosarcomas display typical architectural features of irregular anastomosing vascular channels in the dermis and subcutis. Nuclei are usually hyperchromatic and pleomorphic but the volume of cytoplasm of the neoplastic cells is often small. Diagnosis can be made readily on an adequate biopsy. We recently experienced difficulty diagnosing an angiosarcoma composed predominantly of cells with abundant granular cytoplasm. We were able to compare the present case with sections obtained from the only other reported example. The architectural expression of an anastomosing vascular pattern in areas of tumor, combined with the positive staining for Factor VIII-related antigen (FVIIIIRAg) and Ulex europaeus agglutinin-1 (UEA1) enabled us to make a diagnosis of angiosarcoma. The tumor failed to stain for the other endothelial markers (CD31 and CD34) which were positive in the original case. A marker for lysosomes (CD68) stained the granules in both cases. The granular cell variant of cutaneous angiosarcoma is very rare. Diagnosis is possible by recognizing the typical anastomosing neoplastic vascular channels at the periphery of the lesion, and by use of a combination of lectin (UEA1) and immunohistochemical (FVIIIIRAg, CD34 and CD31) endothelial markers.


Cutaneous angiosarcoma occurring on the head of an elderly person is a well known entity. A recently described histologic variant is granular cell angiosarcoma (1). This variant may prove difficult to diagnose because of its resemblance to other granular cell tumors of skin. Thanks to the generous contribution of sections from the authors of the original reported example, we were able to compare clinical and microscopic features of that case with a 2nd case we saw recently. In particular we examined staining characteristics of this variant of angiosarcoma for a series of endothelial markers.

Reports of cases

Present case

A 76-year-old black woman presented to St. John’s Mercy Medical Center in late 1991 with a 6-month history of right facial swelling in the region of the parotid and the right temple. In the parotid region there was an indurated mass measuring 6 x 4 cm that demonstrated "peau d'orange". The 1 x 1 cm temporal mass was compressible and non tender. The lesions had increased in size and shown increased discoloration in the previous month.

Significant medical history included a left modified radical mastectomy in 1989 for moderately differentiated invasive ductal carcinoma with lymph node metastases. The patient received 6 months adjuvant chemotherapy followed by long-term Tamoxifen, with no sign of possible recurrent disease prior to this admission.

Biopsies of the parotid and temporal lesions revealed angiosarcoma and the patient commenced a course of local radiotherapy. She returned to hospital 1 month later with a left pneumothorax which yielded a blood stained pleural effusion. Cytologic examination and cell blocks of the fluid were negative for tumor. X-ray of the chest revealed two nodular densities in the lower lobe of the left lung. CT scan revealed numerous lesions up to 7 cm in diameter throughout the liver, new since a CT study in October 1989. A liver or lung biopsy was contemplated, but the patient’s pulmo-
Angiosarcoma

Fig. 1. Present case. Typical anastomosing vascular channels of angiosarcoma in the superficial dermis, and solid granular cell component in the deep dermis (hematoxylin-eosin, x16).

nary function deteriorated and she died. No autopsy was performed. The sections of the 1989 breast tumor were reviewed and demonstrated an unremarkable invasive ductal carcinoma.

Previous case

The clinical and histologic features of this case have been reported (1). Briefly, the patient was a 72-yr-old man with an ulcerated lesion involving most of the nasal bridge, with spread to the cheek despite resections. He died of bronchopneumonia 12 months after initial presentation, without clinical evidence of metastatic disease. No autopsy was performed. The authors kindly provided us with paraffin sections of the resection specimen for immunohistochemical staining.

Material and Methods

Representative formalin-fixed, paraffin-embedded sections from each case were stained with hematoxylin and eosin and examined. Immunoperoxidase and lectin staining was performed using the avidin biotin technique with diaminobenzidine chromogenic substrate. The biotin-labelled secondary antibody was deleted for the lectin. Dilutions of reagents varied depending on which of the three different laboratories stains were performed. In summary, primary antibodies to FVIIIIRAg (1/8000, Dako Corp., California), AE1/AE3 (1/100, Boehleringer Mannheim, Indiana), EMA (1/20, Dako), Vimentin (1/5, Dako), S100 (1/400, Dako), CD34 (1/30, Becton Dickinson), CD31 (1/30, Dako) and CD68 (1/50, Dako) were used. The biotinylated lectin, UEA1, (1/50, Vector Labs, California) was also used.

Microscopic observations

Present case

The biopsies of the temporal and parotid regions were similar, with a tumor infiltrating dermis and subcutis, separating preexisting adnexa and blood vessels (Fig. 1). The majority of the tumor consisted of loosely cohesive sheets of polyhedral cells with moderately pleomorphic nuclei and abundant finely granular cytoplasm without intracytoplasmic lumina (Fig. 2). Cell membranes were distinct. In the spaces between the irregular aggre-

Fig. 2. Present case. Granular cytoplasm in tumor cells with moderately pleomorphic nuclei, surrounding small vascular spaces (hematoxylin-eosin, × 400).
Fig. 5. Present case. FVIIIIRAg staining of the anastomosing vascular channels in the superficial dermis with normal melanin pigmentation in the epidermis (FVIIIIRAg, × 30).

Fig. 4. Present case. Prominent UEAl staining of the solid mass of granular cells in the dermis (UEAl, x100).

Fig. 3. Present case. FVIIIIRAg staining of the anastomosing vascular channels in the superficial dermis with normal melanin pigmentation in the epidermis (FVIIIIRAg, × 30).

gates of granular cells there were variably sized lakes of erythrocytes. Up to three mitoses per square millimeter were observed. There was patchy central necrosis. At the periphery of the lesion there were thin-walled anastomosing vascular spaces, lined by neoplastic cells with pleomorphic hyperchromatic nuclei, but without the volume or granularity of cytoplasm seen elsewhere in the tumor. Hemosiderin deposition was not prominent. There was a moderate mononuclear inflammatory cell infiltrate at the periphery of the tumor. There was no epidermal hyperplasia.

The cells lining the anastomosing channels at the periphery of the tumor stained with both FVIIIIRAg (Fig. 3) and UEAl. The granular cells in the solid component failed to stain with FVIIIIRAg despite staining of entrapped endothelial cells. UEAl stained the cytoplasmic granules and, less strongly, cell membranes (Fig. 4). Erythrocytes also stained in this solid area thus highlighting the hemorrhagic nature of the tumor. The cytoplasmic granules in scattered groups of tumor cells stained with CD68. This tumor did not stain with CD34 or CD31. The internal control tissues including dermal dendrocytes and normal endothelium were positive for CD34, but endothelial staining by CD31 was only focal (Table 1).

Tissue from the granular cell areas of tumor was retrieved from paraffin and processed for electron microscopy. The granular cells were joined by intermediate junctions, and separated by small amounts of loose interstitium and poorly formed spaces containing erythrocytes. The cells' cytoplasm was packed with membrane-bound granular

Table 1. Summary of lectin and immunohistochemical stains

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* previously reported (1).

f repeated in our laboratory.
Angiosarcoma

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material consistent with autophagic vacuoles. No endothelial-specific Weibel-Palade bodies were identified.

Previous case

The histologic appearance has been described (1). It was similar to the present case with sheets of polyhedral granular cells separated by irregular spaces containing blood. There was an additional solid spindle cell component. All three components stained for UEA-1, but in common with the present case only vascular lining cells stained well for FVIIIRAg. The CD34 and CD31 markers both were characterized by strong membrane staining in the granular cells and spindle cells (Fig. 5 and Fig. 6), in contrast to the present case. There was less prominent staining of the granules in the cytoplasm. CD68 was positive in the granules, in a distribution similar to the present case.

Discussion

The majority of cutaneous angiosarcomas display a typical histologic pattern of interconnected vascular channels lined by variably pleomorphic endothelial cells with hyperchromatic nuclei (2–4). Other patterns may make diagnosis more difficult. There is a histologic spectrum from bland cytologic features and subtle neovascular lumina, to solid masses of poorly differentiated spindle or epithelioid cells. We report a case where the majority of the tumor consisted of cells with ample granular eosinophilic cytoplasm – at first suggesting a differential diagnosis which included several granular cell tumors. The distinctive architectural features, especially at the periphery of the lesion, and the lectin and immunohistochemistry of the lesion led to the diagnosis of angiosarcoma.

The present case is similar to the only other reported case of granular cell angiosarcoma (GCA) (1). Both were primary cutaneous lesions on the head of an elderly patient. Both contained solid granular cells areas in addition to typical anastomosing vascular channels. Both patients died within 12 months of diagnosis; however, the absence of autopsy examinations limited assessment of the role the tumors played in the clinical course. In the present case the presence of lesions in the liver and lungs favored metastatic malignancy. However, one cannot exclude the possibility that these metastases may have been from the

Fig. 5. Previous case. Strong staining with CD34 of both anastomosing and solid areas of the angiosarcoma (CD34, x16).

Fig. 6. Previous case. CD34 staining is concentrated on the cell membranes rather than the granules (CD34, x80).
breast cancer. The short survival suggests similarly poor prognosis for this variant of angiosarcoma when compared with typical cutaneous angiosarcoma. This contrasts with the epithelioid variant's possible better prognosis (5). The multifocal presentation of the present case, on the temporal and parotid regions, is seen in about half of cutaneous angiosarcomas (2).

The differential diagnosis of granular cell tumors of the skin where the granules result from accumulation of lysosomal inclusions has been reviewed recently (6). The most useful feature to distinguish the GCA from other granular cell tumors is the formation of anastomosing vessels with atypical endothelial lining cells. The poorly cohesive solid areas containing blood are not described in the other tumors. GCA lacks the pseudoepitheliomatosus hyperplasia and exceeds the cellular pleomorphism of most granular cell schwannomas. The two GCA were more deeply situated than primitive polyoid granular cell tumors and lacked a collarette. The abundant fibrous stroma of a granular cell leiomyosarcoma was not present in GCA. The absence of keratinization in cells, or clefts between tumor and myxoid stroma, distinguishes the GCA from the granular form of basal cell carcinoma.

In the head and neck, salivary tumors and metastatic renal carcinoma can have granular cytoplasm. This is usually due to oncocytoic change, the mitochondrial origin of which may be difficult to distinguish from the lysosomal accumulation in the cells of GCA. Most oncocyotpic tumors of the salivary gland are benign, and do not have the nuclear pleomorphism of GCA (7). The poorly cohesive solid areas of GCA contrast with the adherent solid areas of an oncocyotic salivary adenoma. A malignant salivary oncocyotic tumor would not contain anastomosing vascular channels lined by atypical endothelium at the periphery. Metastatic renal cell carcinoma is typically deeper dermally, hemorrhagic and highly vascular, but the endothelial cells are not atypical. The usual renal oncocyotoma is a well-differentiated, essentially benign neoplasm, which would not be expected to metastasize to the skin. Less well-differentiated renal carcinomas may, however, contain granular cell areas. The presence of cytokeratin staining with negative endothelial, smooth muscle and neural markers would favor a carcinoma in this situation.

We were able to compare the lectin and immunostaining of these 2 cases. UEAl is more sensitive for identifying endothelium than FVIIIRAg, but needs careful exclusion of epithelial tumors when positive (8). Although there are reports of cytokeratin staining in angiosarcomas (9), it has been our experience that negative cytokeratin and epithelial membrane antigen staining is strong support for the endothelial specificity of UEAl in an individual case (10). Similarly, failure to stain with S-100 antibody helps to exclude the common benign granular cell schwannoma from the differential in a small biopsy where architectural features of vascular differentiation are not identified.

FVIIIRAg is highly specific for endothelium but lacks sensitivity. Investigators have found that staining of normal endothelium varies with the size of blood vessels and is negative in many or most typical angiosarcomas (8, 11). Lack of staining in solid cellular areas is described for FVIIIRAg and UEAl (5, 12). In the present case the cells lining vascular channels stained but the granular cells failed to stain for FVIIIRAg. In the original report, and confirmed in our laboratory, the previous case showed similar results with only focal staining in the granular areas.

There is a family of CD34 monoclonal antibodies. CD34 antibodies are sensitive markers for endothelium (12, 13), particularly for intracytoplasmic neolumina. Unfortunately, there are specificity limitations similar to those of UEAl due to
staining of other normal and neoplastic cells. Dermal dendrocytes, sweat gland basement membrane and hematopoietic progenitor cells stain with CD34 (12–14). Neoplasms which stain include dermatofibrosarcoma protuberans, epithelioid sarcoma, neurofibromas, and some smooth muscle and fibrohistiocytic tumors (15–17). A smooth muscle tumor with granular cytoplasm could enter the differential of GCA. This species of neoplasm was excluded because of the typical angiosarcomatous anastomosing architecture at the periphery of each tumor, as well as the other immunostaining results that supported endothelial differentiation.

CD31 is an antigen of an adhesion molecule found in endothelium. Like CD34, CD31 has mainly been examined in hematopoietic neoplasms. The JC70 type of CD34 marker is preferred for paraffin-embedded tissue. Compared with CD34 and CD31 in the previous case, but absence of tumor staining for both in the present case. This difference between the cases may be due to loss of antigenicity due to preservation artifacts in the present case, but other lectin and immunostains were positive in internal controls. Alternatively, the present tumor may have reached a different stage of differentiation, thereby displaying fewer markers of its endothelial nature. A combination of factors is possible.

CD68 is an antigen derived from alveolar macrophages (18). KPI is an antibody to CD68 which has proven useful in identifying lysosomal-related products. Both hematopoietic and non-hematopoietic tissues containing lysosomes, including benign granular cell tumor (of neural origin) in the skin, stain with KPI (19,20). The staining of the granules in these angiosarcomas further supports the lysosomal rather than macrophage-specific nature of this marker.

Examination of the periphery of granular cell tumors in the skin for the formation of anastomosing vascular channels lined by atypical endothelium is very helpful in appropriately diagnosing those occasional angiosarcomas which present with this morphology. The lectin stain, UEA1, remains useful in the appropriate context for supporting endothelial differentiation. The more recently described markers such as CD34 and CD31 may give impressive results, but they still fail to stain some tumors.

Acknowledgments

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References


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