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Original contribution

Aberrant expression of neuroendocrine markers in angiosarcoma: a potential diagnostic pitfall☆

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Summary Angiosarcomas (AS) are uncommon endothelial malignancies, usually arising from sun-damaged skin in older adults. Although most AS are readily diagnosed by light microscopy alone, immunohistochemistry (IHC) for endothelial markers such as CD31, CD34, FLI1, and ERG plays a valuable adjunctive role. However, IHC studies of AS must be interpreted with caution, as aberrant expression of markers such as cytokeratins, CD30, and CD117 may be seen. We report 3 cases of AS showing aberrant expression of the neuroendocrine markers synaptophysin and/or chromogranin A, previously unreported phenomena. Cases presented as metastatic lesions in the lung of a 48-year-old woman and as primary tumors of the kidney and neck in a 29-year-old and a 51-year-old woman, respectively. All cases expressed synaptophysin and/or chromogranin A, and various neuroendocrine/endocrine neoplasms were strongly considered as diagnoses by the initial evaluating pathologists. Additional morphological study and confirmatory IHC for CD31, FLI1, and ERG established the diagnosis of AS in all cases. Coexpression of synaptophysin and chromogranin A in 1 case suggests that at least some AS show true neuroendocrine differentiation. Awareness of this potential diagnostic pitfall is important for correct diagnosis and treatment of this rare subset of AS.

1. Introduction

Angiosarcomas (AS), uncommon sarcomas showing endothelial differentiation, most often occur in sun-damaged skin in older adults but may also occur in somatic soft tissue, visceral, and osseous locations [1]. Significant subsets of AS occur as secondary complications of therapeutic irradiation, in particular for breast cancer [2], and chronic lymphedema (Stewart-Treves syndrome) [3].

The pathologic diagnosis of AS is generally relatively straightforward provided the tumor shows light microscopic evidence of vasoformation. However, some AS fail to show this feature, presenting instead as poorly differentiated epithelioid or spindled lesions that may mimic a wide variety of other mesenchymal and nonmesenchymal tumors, including carcinomas and various spindle cell sarcomas [1]. In these settings, immunohistochemistry (IHC) has proven to be extremely valuable in establishing the diagnosis of AS using endothelium-associated markers such as von Willebrand

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factor (factor 8–related antigen) [4]; CD31 [5]; CD34 [6]; and, more recently, FLI/ERG proteins [7,8] and claudin-5 [9]. With increased reliance upon IHC for the diagnosis of AS, however, has come awareness of potential immunohistochemical pitfalls, including aberrant expression by AS of various antigens including cytokeratins [10], CD30 [11], and CD117 (c-kit) [12]. Additionally, it has become clear that putative endothelial markers may be expressed by non-AS (eg, CD31 expression in intratumoral macrophages [13], FLI1 expression in adenocarcinomas [14], ERG expression in epithelioid sarcomas [15,16]).

Recently, we saw in consultation a case of miliary metastatic angiosarcoma involving the lung, which was initially mistaken for diffuse idiopathic neuroendocrine cell hyperplasia, chiefly because of strong synaptophysin expression by the neoplastic cells. Prompted by this case, we reviewed our experience with AS showing aberrant expression of neuroendocrine markers, with the goal of raising awareness of this previously unreported diagnostic pitfall.

2. Methods and materials

Approval for this study was granted by the Mayo Clinic Institutional Review Board. All available hematoxylin and eosin–stained and immunohistochemical slides for 3 cases previously coded as "angiosarcoma" showing aberrant expression of synaptophysin and/or chromogranin were retrieved from our institutional and consultation archives and re-reviewed. The clinical features of one of these cases had been previously reported as part of a larger series of AS involving the kidney [17]. Cases 1 and 2 (see below) were originally shown to exhibit synaptophysin and/or chromogranin A expression by immunohistochemistry performed at outside institutions and at the time of their consultative evaluation at our institution (7 and 2 years ago, respectively). Case 3 was a relatively internal case, shown to express neuroendocrine markers during primary evaluation. For the purposes of this study, IHC for cytokeratins (OSCAR, 1/100, Covance, Princeton, NJ, and AE1/AE3, 1/200, Dako Corp, Carpinteria, CA), CD31 (JC/70a, 1/350, Dako Corp), CD34 (QBEnd/10, 1/50, Leica Biosystems Inc, Buffalo Grove, IL), FLI1 (G146-254, 1/50, BD Pharmingen, Franklin Lakes, NJ), ERG (9FY, 1/25, Biocare Medical, Concord, CA), synaptophysin (27G12, 1/50, Leica Biosystems Inc.), and chromogranin A (LK2H10, prediluted, Ventana Medical Systems, Tucson, AZ) was repeated on cases 1 and 2 using heat-induced epitope retrieval and the Ventana Ultraview detection system (Ventana Medical Systems). These IHC studies had recently been performed on case 3 and were not repeated.

Table Immunohistochemical results

Antigen	Case 1	Case 2	Case 3
Synaptophysin	Positive in >75% of cells [a]	Positive in 5%-10% of cells	Positive in >75% of cells
Chromogranin A	Negative	Positive in >75% of cells [b]	Negative
CD31	Positive in >75% of cells	Positive in >75% of cells [b]	Positive in >75% of cells
CD34	Negative	Negative	Negative
FLI1	Positive in >75% of cells	Positive in >75% of cells	Positive in >75% of cells
ERG	Not tested	Not tested	Positive in >75% of cells
Cytokeratins	Negative	Negative	Positive in 25%-50% of cells

[a] Case 1 was positive for synaptophysin by immunohistochemistry performed at 2 outside institutions and by testing at our own institution.

[b] Case 2 was positive for chromogranin A by immunohistochemistry performed at the outside institution, by our own institution at the time of initial evaluation, and on repeat testing at the present time.

3. Results

3.1. Clinical histories

Case 1 presented as multiple pulmonary nodules ranging in size from 0.1 to 1.0 cm in diameter, in a previously healthy 48-year-old woman. Open surgical biopsies were performed of several of these nodules, which were initially interpreted at an outside institution as representing diffuse idiopathic neuroendocrine cell hyperplasia, chiefly on the basis of strong synaptophysin expression by the neoplastic cells, on immunohistochemical studies performed at the outside institution (see below). The patient was subsequently referred to a second outside hospital, where the diagnosis of multicentric pulmonary epithelioid hemangioendothelioma was suggested. Immunohistochemical studies performed at this second outside institution showed the lesional cells to express CD31 and synaptophysin, but not cytokeratins. The case was then referred in consultation to our institution, where the lesions were shown to represent metastatic high-grade AS (see below). Subsequent clinical investigation disclosed a previously occult AS in the C5 vertebral body.

Case 2 occurred as a destructive, hemorrhagic, 3.7-cm-in-greatest-dimension renal mass in a 29-year-old African-American woman. This case was referred in consultation with a suggested diagnosis of high-grade neuroendocrine carcinoma of the kidney owing to strong cytokeratin and chromogranin A expression by the tumor on immunohistochemical studies performed at the outside institution (see below).

The final case (case 3) (initially evaluated at our institution) occurred in a 51-year-old woman with history of previous neck irradiation for treatment of a lymphoma at