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Case Report

Clear cell atypical fibroxanthoma arising from vaginal stump: a case report from unusual location with a history of radiation therapy

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Abstract: Clear cell atypical fibroxanthoma (CCAFX) is a rare variant of superficial undifferentiated pleomorphic sarcoma, and considered as a tumor of intermediate malignant potential with a relatively indolent clinical behavior. The patient was a 70-year-old female, with a history of a surgery and radiation therapy for rectal adenocarcinoma 10 years ago, who underwent incomplete excision for an exophytic mass on the vaginal stump. Histologically, the tumor was composed of polygonal cells with clear vacuolated cytoplasm and enlarged, vesicular nuclei with prominent nucleoli. The tumor cells were immunopositive for CD10, CD68, CD99, vimentin and procollagen-1, but negative for pan-cytokeratin, HMB45, Melan-A, S100 protein, CD117 and smooth muscle actin. Based on histomorphologic, immunohistochemical, and ultrastructural findings, a diagnosis of CCAFX with histocytic and fibroblastic differentiation was rendered. The tumor recurred during the follow-up period of 4 months. Recognition of CCAFX in the unusual location is important for the proper diagnosis and optimal management.

Keywords: Clear cell atypical fibroxanthoma, undifferentiated pleomorphic sarcoma, vagina

Introduction

Atypical fibroxanthoma (AFX) is also known as a superficial variant of undifferentiated pleomorphic sarcoma (UPS). Although AFX has been recently classified as an undifferentiated pleomorphic sarcoma based on its histological similarity, this tumor has a more favorable prognosis with a rare ability for local recurrence or metastasis. AFX is predominantly presents on sun-exposed skin areas, such as the head and neck region, of elderly individuals. It may also involve non-sun-exposed areas, such as the trunk or extremities, usually in younger patients [1]. Risk factors for this tumor include UV exposure and history of radiation [1], trauma [2], or transplant [3]. AFX has been described as having clear cell, granular, myxoid, keloidal, and pigmented hemosiderotic variants [4]. Among these variants, clear cell atypical fibroxanthoma (CCAFX) is a very rare with only 12 cases reported in the literature. The clear cell appearance of neoplastic cells is due to the presence of numerous lipid vacuoles within their cytoplasm. Recently, we experienced a 70-year-old woman with an exophytic mass presenting with rapid growth on the vaginal stump. To our knowledge, this is the first case of CCAFX involving the vaginal mucosa with a history of radiation.

Case report

A 70-year-old female transferred to our hospital presenting with an exophytic mass on the vaginal stump. She had a medical history of rectal adenocarcinoma 10 years prior, for which she underwent a low anterior resection and total hysterectomy with bilateral salpingo-oophorectomy and radiation therapy. She was well with no evidence of rectal cancer until this presentation. Pelvic computed tomography (CT) showed a well-defined 4.5-cm sized mass on the vaginal stump, which was undetected by a previous pelvic CT 6 months prior (**Figure 1A**). Under the impression of a perirectal abscess, a

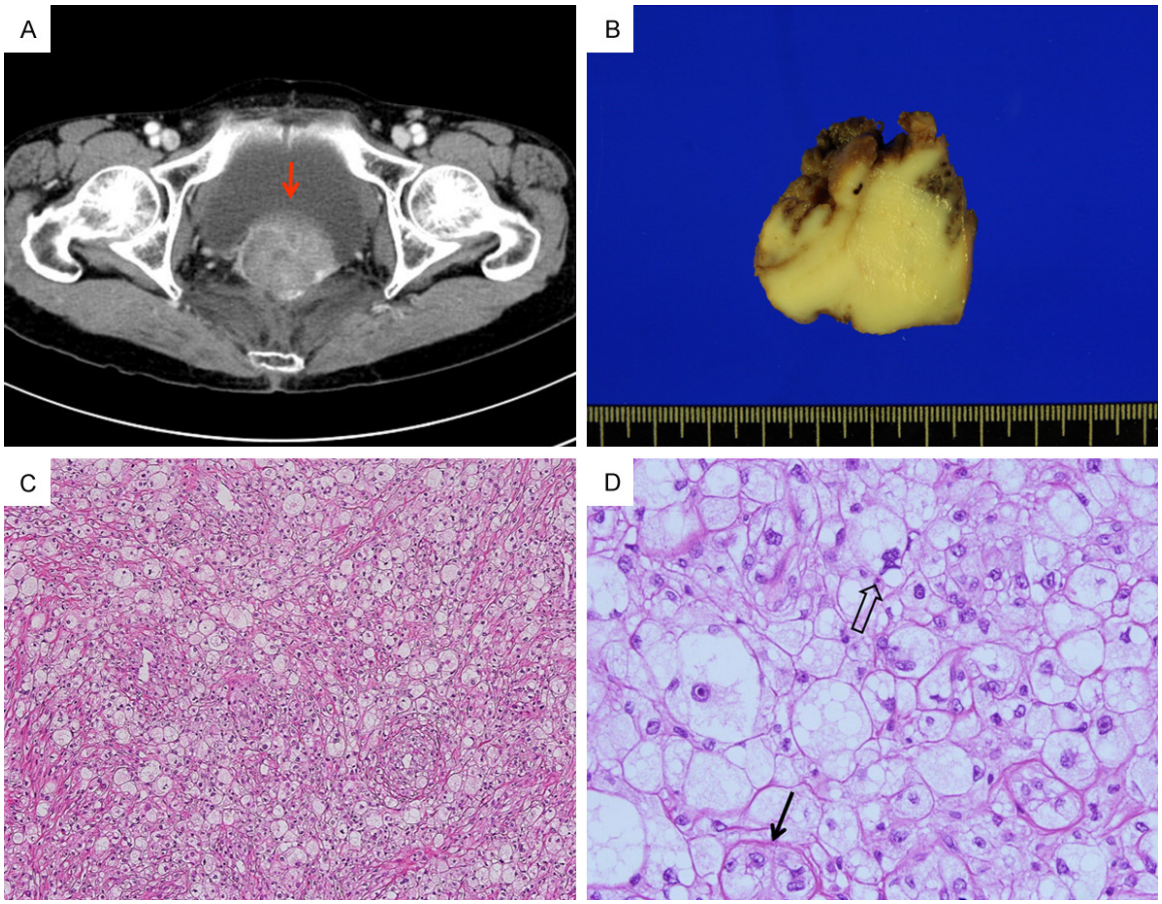

Figure 1. Pelvic computed tomography (CT) shows a well-defined 4.5 cm mass on the vaginal stump (red arrow, A). The cut surface of the mass is homogenous, yellowish white and glistening with surface ulceration (B). The tumor shows solid sheets or vaguely fascicular pattern with ectatic vasculatures (C). The tumor cells are composed of polygonal or epithelioid cells with abundant clear vacuolated cytoplasm and enlarged, vesicular nuclei with occasionally prominent nucleoli. Scattered bizarre cells (open arrow) and multinucleated giant cells (closed arrow) are identified (D).

vaginal mass excision was performed. The resected mass was whitish tan and glistening with surface ulceration. The cut surface was yellowish white and firm with multifocal hemorrhage (**Figure 1B**). Histologically, the tumor showed solid sheets or vaguely fascicular pattern with ectatic vasculatures (**Figure 1C**). The tumor was composed of polygonal or epithelioid cells with abundant clear vacuolated cytoplasm and enlarged, vesicular nuclei with occasionally prominent nucleoli. Scattered bizarre cells and multinucleated giant cells were identified (**Figure 1D**). The tumor had focal necrosis and increased mitotic figures (8/10 high-power fields [HPF]). Immunohistochemically, the tumor cells were positive for CD10 (1:100, NovocastraTM, Newcastle, UK), CD68 (1:2000, Dako, Glostrup, Denmark), CD99 (1:200, Dako, Glostrup, Denmark), vimentin (1:500, Zymed, San Francisco, CA) and procollagen-1 (PC-1; 1:50, Bioscience Research Reagents [formerly Chemicon], Temecula, CA) (**Figure 2A-D**), but negative for cytokeratin (1:200, Zymed, CA), HMB45 (1:50, Dako, Glostrup, Denmark), Melan-A (1:50, Novo, Newcastle, UK), S100 protein (1:100, Zymed, CA), CD117 (1:400, Dako, Glostrup, Denmark), TFE3 (1:100, Cell Marque, Rocklin, CA), MDM2 (1:100, Zeta, Arcadia, CA), and smooth-muscle actin (1:200, Dako, Glostrup, Denmark). The tumor cells showed about 20% immunoreactivity for p53 (1:1500, Dako, Glostrup, Denmark; **Figure 2E**) and the Ki-67 (1:200, Dako, Glostrup, Denmark) labeling index was approximately 20%. PAS and d-PAS stains revealed no glycogen in the tumor cells. The differential diagnoses, such as metastatic clear cell renal cell carcinoma, clear cell variant squamous cell

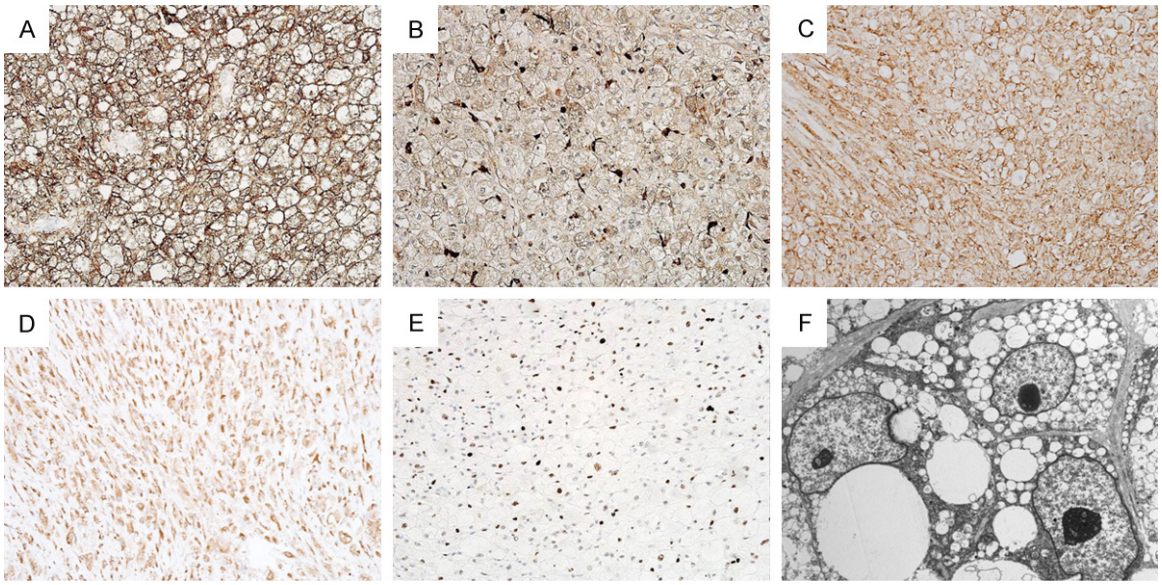

Figure 2. The neoplastic cells in the current case are immunopositive for CD10 (A), CD68 (B), CD99 (C), and procollagen-1 (D). These tumor cells also show increased immunoreactivity for p53 (E). On electron microscopy, the polygonal cells have numerous lipid vacuoles in their cytoplasm and ovoid nuclei with irregular nuclear outlines and prominent nucleoli (F).

Table 1. Clinicopathologic features of previously reported cases of clear cell atypical fibroxanthoma

Case	Age	Sex	Site	Size (cm)	Radiation history	Treatment	Adjuvant treatment	Prognosis	Reference/Year
Murali et al.	67	M	Ear	1.0	n/a	Excision	n/a	n/a	J Cutan Pathol./2006
Crowson et al.	88	M	Scalp	0.7	n/a	Excision	n/a	n/a	J Cutan Pathol./2002
	77	M	Forearm	1.1	n/a	Excision	n/a	n/a	
	78	M	Temple	0.8	n/a	Excision	n/a	n/a	
Santander R et al.	90	F	Cheek	2.5	n/a	Excision	n/a	NR (18 mo)	Histopathology./1999
Requena et al.	81	M	Temple	4.0	n/a	Excision	n/a	NR (2 yrs)	J Cutan Pathol./1997
	73	M	Cheek	2.0	n/a	Excision	n/a	NR (1 yr)	
Patterson JW et al.	87	M	Dorsum of hand	1.0	n/a	Excision	n/a	NR (3 mo)	J Dermatol Surg Oncol./1987
Cai JP et al.	63	F	Forearm	n/s	n/a	Excision	n/a	n/a	J Cutan Pathol./2004
Kemmerling R et al.	86	F	Nose	1.4	n/a	Excision	n/a	n/a	Pathol Res Tract./2009
Suarez-Vilela D et al.	86	M	Right ear	1.0	n/a	Excision	n/a	n/a	Case Rep Dermtol./2010
Bedir R et al.	74	M	Right shoulder	2.5	n/a	Excision	n/a	NR (1 yr)	J Clin Diagn Res./2014
Current case	70	F	Vaginal stump	4.5	Y (10 yrs ago)	Excision	N	Recurrence (4 mo)	

n/a, not available; Y, yes; N, no; NR, No recurrence.

carcinoma, dedifferentiated liposarcoma, malignant melanoma, and perivascular epithelioid cell tumor (PEComa) were included, but these could be easily excluded by immunohistochemical findings. On transmission electron microscopy, the polygonal cells had ovoid nuclei with irregular nuclear outlines and prominent nucleoli and numerous lipid vacuoles in the cytoplasm (**Figure 2F**). No definite cell junction was observed. Based on the morphology, history of radiation treatment, and immuno-profiles, the diagnosis of CCAFX was rendered. During the 4-month follow-up period, she had a rapid recurrence of the tumor due to incomplete excision. A re-excision of the recurrent tumor was performed, but an adequate margin was not secured.

Discussion

AFX belongs to a group of fibrohistiocytic tumors and is considered to be a superficial

variant of UPSs. In most cases, the tumor superficially locates on sun-exposed skin in the head and neck of elderly patients, and presents most often as a rapidly enlarging exophytic mass. When the tumor affects younger individuals the distribution is different with more smaller tumors located on non-sun-exposed skin, such as the trunk and limbs [4]. AFX has also been reported in unusual mucosal locations such as the ethmoid sinus [5], the oral mucosa [6], the eyelid [7], the cornea [8], and the perianal area [9]. Classical AFX is composed of pleomorphic, epithelioid, or spindle cells arranged in a hapazard, vaguely fascicular, or storiform patterns with circumscribed or laterally infiltrative border.

CCAFX is a rare variant of AFX and only 12 cases have been reported in the English literature, all of which involved the superficial dermis in elderly patients. The clinicopathologic features of these previously reported cases of CCAFX are summarized in **Table 1**. Except for three cases that arose on the right shoulder, forearm, and dorsum of the hand, the majority of CCAFX cases were located on sun-exposed head area. All of the previously reported CCAFXs developed on the skin; however, in our current case the lesion was located in an unusual mucosal site. Including the current our case, CCAFX occurs more frequently in males (n=9) than in females (n=4) with a median age of 78 years (range: 63-90 years). The tumors show rapid growth after detection, ranging from 2 weeks to 6 months [10]. Although Fretzin et al. [1] have reported that 4.2% of AFXs develop in a previous site of radiation and the latency period is longer than 10 years, the reported CCAFX cases did not describe any history of radiation therapy.

The differential diagnosis of AFX includes benign fibrous histiocytoma (dermatofibroma), especially rare variants of clear cell fibrous histiocytoma, or lipidized fibrous histiocytoma. Dermatofibroma is histologically distinct from CCAFX due to the presence of sclerotic collagen bundles intermingled in the typical portion at the periphery of the tumor and scant mitoses [11]. Recently, several immunomarkers have been reported as useful tools for the diagnosis of AFX. While CCAFX and dermatofibroma display immunopositivity for CD10 and CD68, PC-1 has better sensitivity (87%) for the identification of AFX [12, 13]. Our current case showed immunopositivity for CD68, vimentin, CD10, and PC-1. CD10 expression has been seen in fibrocytes and dendrocytes. Furthermore, PC-1 is a precursor of collagen synthesized by fibrocytes and myofibrocytes and the expression of PC-1 indicates a fibrocytic differentiation or lineage. De Feraudy reported that both PC-1 and CD10 immunostains are useful markers for distinguishing these tumors from AFX [13]. CD99, CD68, and vimentin are also expressed in CCAFX [10]. Although the current tumor superficially resembles a benign neoplasm such as xanthoma or fibrous histiocytoma, this lesion showed a rapid growth, focal necrosis, and increased mitosis, with increased immunopositivity for p53 and an increased Ki-67 labeling index (20%), indicating malignancy. CCAFX must be distinguished from other malignant neoplasms, such as metastatic clear cell renal cell carcinoma, clear cell variant squamous cell carcinoma, pleomorphic liposarcoma, balloon cell malignant melanoma, leiomyosarcoma with clear change, and PEComa. However, the tumor had no immunoreactivity for cytokeratin, MDM2, SMA, or melanocytic makers such as HMB45, S100 protein, and melan-A. Our patient's tumor had extensive clear vacuolated cell areas with scattered bizarre and multinucleated giant cells and did not stain with PAS, excluding the possibility of leiomyosarcoma and metastatic clear cell renal cell carcinoma. Electron microscopic findings of the polygonal epithelioid cells revealed numerous lipid vacuoles in the cytoplasm and irregular nuclear outlines with prominent nucleoli. The cells also had non-specific microfibrils and micro-organelles, indicating myofibroblastic nature of the tumor cells.

The histomorphology of the tumor in our current case resembled previously reported cases of CCAFX; however, the morphologic atypia was insufficient to diagnose this tumor as high-grade UPS.

AFX and UPS have been suggested to be a spectrum or progression of the same type of malignancy and both terms have interchangeably used [14]. Despite the histological similarity between AFX and UPS, the two tumors have different clinical behaviors with a more favorable prognosis and a low rate of recurrence in the former. Several molecular studies have shown that the two entities possess molecular differences. The most frequent alterations

involving deletions on chromosomes 9p and 13q in both entities might suggest a common pathogenetic pathway, although significant differences in the genetic alterations between the two tumor types have been reported [15]. UPS has more complex cytogenetic abnormalities, including deletions, gains, and amplifications [4]. UV-induced p53 mutations in AFX have already been postulated [16]; however, MDM2 amplification in UPS might be attributable to TP53 inactivation or downregulation [4]. Sakamoto et al. described H- and K-Ras gene mutations being frequently detected in UPS, but similar mutations have not emerged in AFX. These findings accordingly may play an important role in the pathogenesis of the two tumors [17].

A complete wide excision with a 1-cm lateral free margin is the recommended treatment for AFX. Local recurrence occurs in 7-12% of surgical excision cases due to an inadequate surgical margin. Routine postoperative follow-up every 6 months for a minimum of 2 years is also recommended; however, radiotherapy is not recommended and not necessary. Although high-grade UPS requires surgical excision with a 3- to 5-cm free margin and dissection of regional nodes, local recurrence and/or metastasis usually occurs in 40-50% of cases primarily within 2 years. Postoperative follow-up every 3-4 months for the first 2 years and then every 6 months until 5 years is recommended, and adjuvant radiotherapy may be required [18].

Based on the morphology, history of radiation therapy, and immunoprofiles of our current case, the diagnosis of CCAFX is consistent with the tumor being a superficial variant of UPS.

This case underwent incomplete excision and rapid local recurrence occurred, but metastasis was not evident during the 4-month follow-up period. An intermediate prognosis was suspected in this case because of the unusual tumor location, larger size, focal necrosis, history of recurrence, and inadequate resection margin. CCAFX is a diagnostic challenge for pathologists, and the recognition of this entity should prevent an inaccurate diagnosis that would otherwise result in incomplete excision or overtreatment.

In summary, to the best of our knowledge, this is the first report of a CCAFX case in which the tumor occurred in the mucosa of the vaginal stump after hysterectomy and bilateral salingo-oophorectomy with radiation therapy.

Disclosure of conflict of interest

None.

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