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Case Report

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Epithelioid Angiosarcoma of the Adrenal Gland. Report of a Case and Review of the Literature

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Abstract

Background: Primary mesenchymal neoplasms of the adrenal gland are rare, and a malignant one is an extraordinary finding. Angiosarcomas are uncommon neoplasms and account for less than 1% of sarcomas. Due to their rarity, they can easily be misdiagnosed, both by the clinician and the pathologist.

Case report: We present a case of 55 year old man with primary epitheloid angiosarcoma of the right adrenal gland and a review of the literature in an attempt to better define the clinical and pathological features of these neoplasms and their biologic potential. Immunohistochemical analyses were performed using endothelial cell markers (CD31, CD34 and Factor VIII). The analyses showed focal positivity of tumor cells, especially CD31 and weak focal positivity for tumor cells of Cytokeratin 18. The review of the literature showed 32 cases described up-to-date.

Conclusion: The present case emphasizes problems in differential diagnosis that arise from its epithelioid differentiation. We show review of the relevant literature which underlines the poor clinical outcome of adrenal angiosarcoma despite the adequate surgical treatment.

Introduction

Primary mesenchymal neoplasms of the adrenal gland are uncommon, especially the malignant ones. Angiosarcomas are rare neoplasms and account for less than 1% of sarcomas. They occur primarily in the soft tissues and skin of elderly people; the head and neck region is one of the more common sites. Angiosarcomas have been reported as primary neoplasms in numerous other sites, including breast, thyroid, heart, lung, pulmonary artery, liver, spleen, kidney, adrenal gland, uterus, ovary, vagina, testis, bone, and serous membranes [1-14].

Rare cases of angiosarcoma have been associated with germ cell tumors. Angiosarcoma may develop in the setting of chronic lymphedema, after irradiation, or after exposure to vinyl chloride, thorotrast, arsenic, anabolic steroids or foreign bodies [6,15-17]. Malignant vascular neoplasms of the adrenal gland are unique when speaking of their appearance, both macro and microscopically. The histological appearances of angiosarcoma vary with diverse patterns of growth, including papillary, spindled, and epithelioid morphologic features. Epithelioid angiosarcomas may demonstrate sheet-like, tubular, or nested

growth patterns with only focal vascular differentiation. This histological appearance, coupled with immunoreactivity for cytokeratins and epithelial membrane antigen, may lead to misdiagnosis as metastatic carcinoma.

In order to provide better distinction and identification of the clinical and pathological characteristics of these neoplasms we performed a review of the available literature. We tried to determine the optimal surgical treatment and to assess the factors that may predict the prognosis and the overall survival of these patients.

The aim of this case report is to report a rare neoplasm with the diagnostic difficulties and the therapeutic approaches.

Case Report

A 55-year-old man presented at our clinic reporting a dull constant pain lasting for ten months in the right part of abdomen irradiating in the right lumbar region and to the back, and a of 8.5 kilogram weight loss in the last 4 months. Complete blood count showed severe anemia and elevated leukocytes count. He was a smoker with up to one pack of cigarettes per day. The Computer Tomography scan showed a tumor mass extending from the right lobule of the liver to the upper pole of the right kidney. The kidney was pushed caudally but seemed intact. The tumor was measured 10 centimeters at its greatest diameter and had several calcifications inside (Figure 1). Resection of the right adrenal gland was performed and a solid and hemorrhagic mass was removed. Microscopic examination and immunohistochemical analyses were consistent with the diagnosis of epitheloid angiosarcoma that originated in the right adrenal gland.

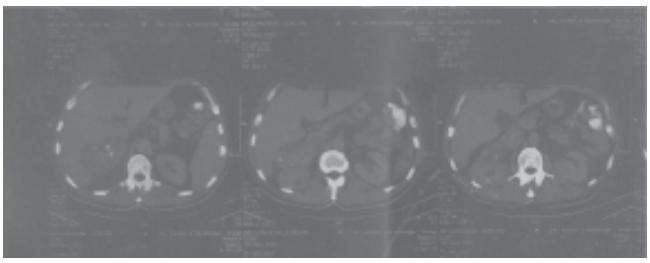

Figure 1: Computer tomography studies revealed formation pushing the right kidney caudally but during the operation the kidney had no tumor invasion.

The Computer Tomography scan did not show tumor presence in others sites throughout the body. There was no splenomegaly, hepatomegaly nor any adenopathies. After the surgery and the removal of the tumor, adjuvant chemotherapy or radiotherapy was not taken into consideration because no positive surgical margins were found.

The patient follow up was made 3 and 6 months postoperatively. The patent continued to lose weight with further 3 kilograms in 3 months. On the second check up he had suspicion for pulmonary metastases confirmed with a second computer tomography scan. Irradiation and chemotherapy were initiated with a small impact on the tumor. The patient died 12 months after the operation.

The surgical specimen was routinely fixed in 10% formalin fixative. Specimens obtained from the tissue were embedded in paraffin blocks and processed in a routine paraffin procedure. Slices with a thickness of 5ì ?were made for routine Hematoxyllin-Eosin staining and later for immunohistochemical staining. Immunohistochemical analyses were performed on paraffin sections using the EnVision+ System-HRP (DAB) using the following antibodies (Table 1):

Table 1: Antibodies used in the immunohistochemical analyzes.

Antibody	Manufacturer	Clone	Pretreatment	Dilution
CD31	DAKO	JC70A	DAKO target retrieval solution pH9	1:50
CD34	DAKO	QBEnd-10	DAKO target retrieval solution pH9	1:50
Factor VIII	DAKO	F8/86	DAKO target retrieval solution pH6	1:100
Cytokeratin Wide Spectrum	DAKO	34βE12	DAKO target retrieval solution pH9	1:700
Cytokeratin 18	DAKO	DC10	DAKO target retrieval solution pH9	1:50
Cytokeratin 19	DAKO	RCK108	DAKO target retrieval solution pH9	1:50
Smooth muscle Actin	DAKO	HHF35	DAKO target retrieval solution pH9	1:100
Neuron Specific Enolase	DAKO	BBS/NC/VI-H14	DAKO target retrieval solution pH6	1:100
Chromogranin	DAKO	DAK-A3	DAKO target retrieval solution pH9	1:100

The gross resection revealed tumor mass weighing 240 grams, and measuring 12x9x5.5 centimeters. The surface of the mass was lobulated and on cut surface the tumor had grayish-brown color with foci of necrosis and hemorrhage. It seemed as if it was packed in a

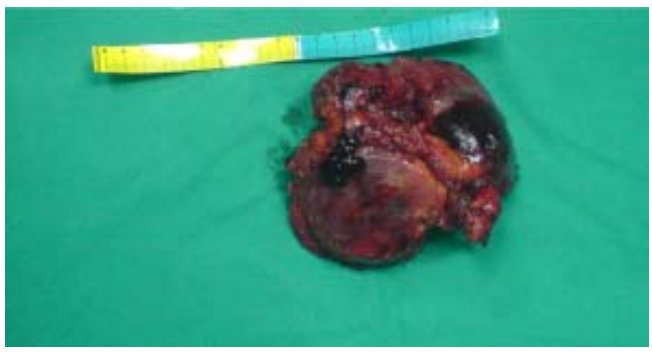

Figure 2: Macroscopic view of the removed tumor.

pseudocapsule and had several cysts and calcifications when resected in half (Figure 2).

Microscopic examination showed different pictures. The dominant one was that of a cellular lesion where tightly packed, highly pleomorphic cells, surrounded vascular areas with foci of pseudoglandular structures. There were areas of collagenous stroma, and areas with tumor necrosis. Rarely there were sclerotic areas and foci of tightly packed blood vessels resembling capillary hemangioma. The vascular areas showed intravascular proliferation of tumor cells with rare foci of tumor embolus formations.

Diagnostic differentiation difficulties occured on standard Hematoxyllin-Eosin stain with features of cortical suprarenal carcinoma, malignant pheochromocytoma and epitheloid angiosarcoma (Figure 3).

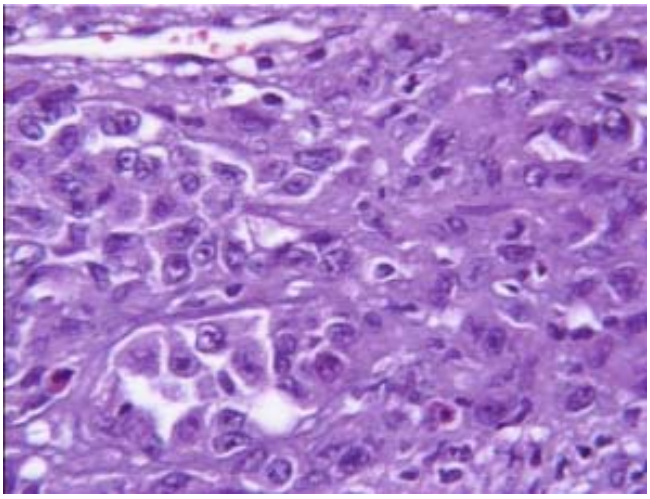

Figure 3: HEx100, anaplastic epitheloid cells lining vascular spaces.

Additional immunohistochemical analysis was performed using endothelial cell markers (CD31, CD34 and Factor VIII) that showed focal positivity of tumor cells, especially CD31. Epithelial markers (Cytokeratin Wide Spectrum, Cytokeratin18 and Cytokeratin 19) did not show positivity in tumor cells, with the exception of Cytokeratin 18 that showed only weak focal positivity of tumor cells. Smooth muscle actin showed focal positivity only in solid nests of tumor cells, while neuroendocrine markers (Neuron specific enolase and Chromogranin) were negative in tumor cells (Figures 4-A, 4-B, 4-C).

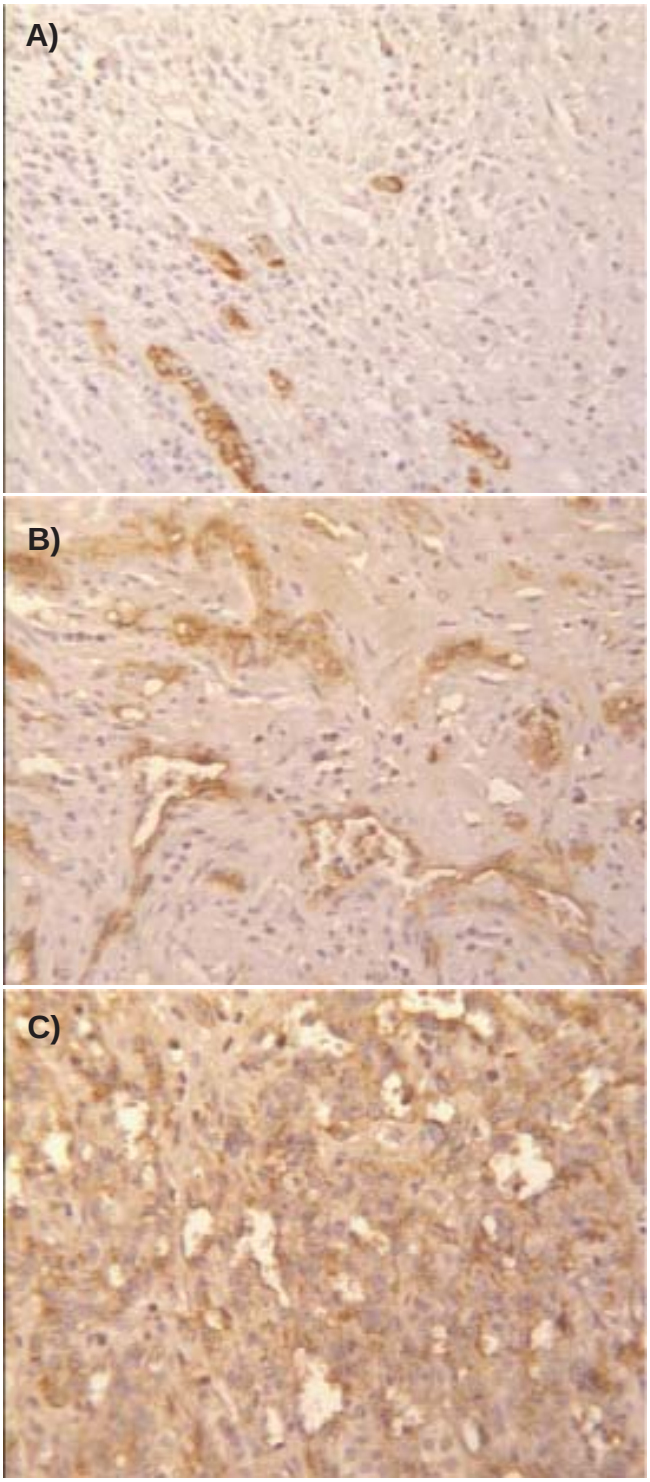

Figure 4: A) CK18x200, focal positivity of tumor cells on this epithelial marker; B) CD34x200, positivity of tumor cells surrounding vascular spaces; C) CD31x200, strong positivity of tumor cells.

Discussion

Angiosarcomas are rare tumors that represent less than 1% of all sarcomas. The most common sites are skin and soft tissue; however, about one quarter of cases are found in other locations, such as breast, liver, bone, and

Table 2: Cases reported in the literature.

Author, year published Ref.	No. of cases	Gender, Age	Immunohistochemistry	Follow up
Rasore-Quartino 1967 [18] *	1		no immunohistochemical diagnosis	
Kern WH al. 1968 [19] *	1		no immunohistochemical diagnosis	
Kareti et al. 1988 [20]	1	Male, 54	Immunoreactivity for keratin	tumor recurrence 7 months after surgery; patient died 4 years after initial operation
Caplan et al. 1991 [21]	1	Male, N/A	N/A	no recurrence 1 yr postoperatively
Bosco PJ et al. 1991 [22]	1	Male	Immunoreactivity for keratin	Liver metastases
Livaditou A et al. 1991 [23]	1	Male, 59	Immunoreactivity for keratin	patient died due to postoperative complications
Ben-Izhak O et al. 1992 [24]	1	Male	Immunoreactivity for cytokeratin, Factor VIII positivity	patient died after surgery
Fiordelise S et al. 1992 [25]	1	Male, 67	Immunoreactivity for keratin	quick fatal progression of disease
Schwenk et al 1994 [26]	1	Male, 50	Immunoreactivity for keratin	Jejunal metastases patient died 9 months after diagnosis was made
Wenig et al 1994 [27] **	8	5 females 3 males, 41-85	Immunoreactivity for keratin; CD31 positivity	3 patients died with metastatic disease, 1 patient died in the immediate postoperative period, 1 case was found incidentally at autopsy, 3 patients alive, without disease 6 to 13 years after initial resection
Jochum W et al. 1994 [28]	1	Male	Immunoreactivity for cytokeratin	Bone metastases
Mc Cleary AJ. 1994 [29]	1	Male	Immunoreactivity for keratin	Pleural metastases
Sasaki R et al. 1995 [30]	1	Male, 62	Immunoreactivity for keratin	patient died of pulmonary dysfunction 42 days after the operation
Abboud E et al. 1999 [31]	1	Female, 65	Factor VIII and vimentin positivity, focal positivity for pancytokeratin.	N/A
Croitoru AG et al. 2001 [32]	1	Male, 63	Factor VIII positivity	Patient died 1.5 yrs postoperatively
Ferrozzi F et al. 2001 [33]	1	Male, 67	Factor VIII positivity	Lung metastases
Inviti C et al. 2001 [34]	1	N/A, 34	CD31, Factor VIII positivity	no recurrence 6 months postoperatively
Kruger S et al. 2001 [35]	1	Male, 70	Immunoreactivity for keratin	patient died due to postoperative complications
Rodriguez-Pinilla SM et al. 2002 [36]	1	Male, 61	CD31 positivity	no recurrence 3 yrs postoperatively
Mayayo Artal E et al. 2002 [37]	1	Male, 60	CD31 positivity	no recurrence 6 months postoperatively
Pasqual E et al. 2002 [38]	1	Female, 70	CD31 positivity	no recurrence 1.5 yrs postoperatively
Sidoni A et al. 2003 [39]	1	Male, 60	Factor VIII and CD31 positivity	no recurrence 3 yrs postoperatively
Galmiche L et al. 2004 [40]	1	Male, 69	CD31 positivity	no recurrence 1 yr postoperatively
Azurmendi Sastre V et al. 2004 [41]	1	Male, 59	CD31 positivity	no recurrence 2 yrs postoperatively
Gambino G et al. 2008 [42]	1	Female, 49	CD31, CD34 and Factor VIII positivity, Immunoreactivity for keratin	no recurrence 1 yr postoperatively
Total	32			

* two cases not taken into consideration because of lack of immunohistochemical analyzes; **Wenig et al. described nine cases (eight new cases plus Karetis' case).

spleen. Epitheloid angiosarcomas of the adrenal gland are extremely rare neoplasms. There are only 32 reported cases up to date (Table 2).

The etiology of the epitheloid angiosarcoma remains unknown. There are only four cases described in the literature where the malignancy could be linked with prolonged exposure to arsenic containing insecticides and presence of mesenteric fibromatosis. Not any other connection nor correlation with a family history of adrenal neoplasms (suggesting Multiple Endocrine Neoplasia syndrome), a prior history of abdominal radiotherapy or long-term androgenic anabolic steroid treatment could be found [27,28].

The disease generally affects more men than women (21 men, 8 women, 1 not specified) with a wide age range from 34 to 85 years, predominantly patients in the sixties and seventies of their life. The disease usually starts with pain and presence of abdominal mass, followed by significant weight loss, fever episodes and weakness.

In six cases the disease is asymptomatic but in four cases is associated with paraneoplastic syndrome and distant metastases to bone and liver [22,28]. One patient had an unusual association with Cushing disease while one patient had accidentally found adrenal tumor [32, 34]. In the sixth asymptomatic patient, the angiosarcoma was revealed after surgery for abdominal trauma and suspected hepatic rupture was performed [42].

Rasore-Quartino and Kern published the first two cases, in the late sixties, but because of lack of immunohistochemical analyzes are excluded from this study [18, 19]. The first case confirmed by immunohistochemical staining was published in 1988 by Kareti [20]. The patient died 4 years after adrenalectomy and wide en bloc resection without evidence of disease. Several single case reports followed later after until Wenig et al. described the largest study in 1994 where 9 cases of adrenal angiosarcoma were analyzed (8 new cases plus one previously published by Karety) [21-27]. In this study done at the Armed Forces Institute of Pathology in Washington, USA, three patients died with metastatic disease, 1 patient died in the immediate postoperative period, 1 case was found incidentally at autopsy and 3 patients were alive without evidence of disease from 6 to 13 years after initial resection. Until 2009, 15 more cases were reported [28-42].

Macroscopically the tumors varied from well-circumscribed to invasive retroperitoneal masses, solid to

cystic, with dimensions from 5 to 16 centimeters at its greatest diameter. Our case showed a solid mass with 12 centimeters in the greatest diameter. All the cases had tendency toward an epithelioid appearance. Among them 19 had immunoreactivity for keratins was while only 3 were negative [22-24,27,28,31,35-42]. The finding of reactivity for cytokeratin is typical of epithelioid morphology and is believed to represent aberrant or "atavistic" expression. Factor VIII and CD31 positivity was detected in 7 cases and 16 cases, respectively [24, 27, 31-42].

Prompt preoperative diagnosis is very complex since they can appear well circumscribed and non contrast-enhancing advocating a benign, non-neoplastic formation. Its irregular histological and immunological attributes as well as its relatively low incidence can make pathologists to misinterpret it for adrenal epithelial neoplasms.

In the clinical practice this neoplasms should always be differentiated from other vascular neoplasms, pheochromocytoma, adrenal cortical carcinoma, metastatic adenocarcinoma, metastatic malignant melanoma and other metastatic tumors as well as from benign neoplasms like adrenal adenomas with hemorrhage and epithelioid hemangioendothelioma [27,32].

The safest and easiest way to confirm or rule out this malignancy is by using immunohistochemistry. Endothelial-related markers (CD34, Factor VIII antigen and CD31) must be used in the antigen panel of these tumors, following their limitations in terms of sensitivity and specificity [27].

In our case radiographic studies were performed to exclude malignancies in soft tissue or other internal organs. Microscopically it matched into the epithelioid variant of angiosarcoma. It was positive for cytokeratin 18 and reacted positively for CD31 and CD 34.

The adrenal angiosarcoma is malignant neoplasm that can invade surrounding organs and tissue as well as metastasize in distant sites. Seven reported cases had metastasized, one to bone and liver [28, 42], one to the pleura [29], one to the jejunum [26] and three to the lung [33].

The treatment of patients with adrenal angiosarcoma is still controversial, because of the limited experience with this tumor. After reviewing of the literature we found 18 cases that were exclusively treated by adrenalectomy [22, 25, 17, 29-31, 35-42] associated with accessory splenectomy [27] or nephrectomy [25, 40, 41]. After the surgery eight patients were alive and well with no recurrence after 6 months [34,37] and 1 [21, 40, 42], 1.5 [38], 3 [36] 11 and 13 years respectively [27]. The follow-up period for two patients was not specified [22, 31]. We found four patients that died due to post-operative complications with evidence of recurrent disease in just one case [23, 27, 29, 30, 35]. Four patients received only surgical treatment but died with disease [25, 27]. In two cases chemotherapy was given after the surgical treatment. One patient died without evidence of disease 4 years after surgery and the other one lived two years longer with no evidence of disease [27].

Our patient, presented with symptoms of persistent dyspnea, nine months after the operation, which lead us to do a Computer Tomography scan of lungs. It revealed a solid mass in the right apical lobe of lung, as well as larger one in the antero-basal part of the lung. We started chemotherapy but the patient died three months after the initiation of the chemotherapy because of the primary disease with symptoms of cardio respiratory failure one year after the initial treatment.

In one case, radiation therapy was started following adrenalectomy with no results published so far.

There were three patients that developed metastases after the surgery was performed, identically to our case. One of them died postoperatively within one month of the intervention, the second died with disease 1 year after treatment and the third was alive with no evidence of disease after 11 years follow-up. One patient received chemotherapy and died with no evidence of disease 4 years after surgery. There are no records for the case that had metastases to the bones and liver.

Epithelioid angiosarcoma of the adrenal gland may mimic much more common primary and secondary tumors and, in view of cytokeratin positivity, especially metastatic carcinoma. Despite its rarity, knowledge of its existence is important as its pathobiologic characteristics may differ markedly from other primary and metastatic adrenal neoplasms. Because of the infrequency of this entity optimal therapy other than surgical eradication is difficult to determine. The complete surgical resection of the adrenal gland with or without any surrounding tissue or organ infiltrated with the tumor has good outcome despite the biology of this tumor. Some cases may have been detected at an early enough stage to enable surgical cure. In view of the aggressive nature of angiosarcoma in all sites, adjuvant therapy appears justified for patients in whom complete surgical extirpation cannot be ensured. The complete eradication combined with 3 to 6 months control intervals are essential for detection of presence of

local recurrence or distant metastases and their treatment with adjuvant chemo or radiotherapy. Presence of local or distant metastases at the time of the primary detection of the tumor or in the first 6 months postoperatively, is negative prognostic parameter that shortens the overall survival of the patients.

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