CASE REPORT

Epithelioid angiosarcoma arising in schwannoma of the kidney: report of the first case and review of the literature

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Abstract

Background: Schwannoma and angiosarcoma are infrequent pathologies that have been rarely reported in the kidney. Angiosarcoma is an uncommon malignant tumor presenting a recognizable vascular differentiation. It can develop in any site but the most common locations include the skin, soft tissues, breast, bone, liver, and spleen while renal localization has been very rarely reported in the literature. Schwannoma is a benign peripheral nerve sheath tumor composed of cells with the immunophenotype and ultrastructural features of differentiated Schwann cells. It has a wide anatomical distribution but the most frequent locations include subcutaneous tissues of the extremities and the head and neck region and the retroperitoneal and mediastinal soft tissues. The occurrence of an angiosarcoma in a pre-existing schwannoma is an extremely rare event with <20 cases reported in worldwide literature. In the present study, a renal case of angiosarcoma arising in schwannoma is presented with a detailed review of the pertinent literature.

Case Presentation: A 56-year-old man was admitted with a few days history of lower back pain and hematuria. Abdominal ultrasound showed a mass inside the left renal medulla. Subsequent imaging investigations with computed tomography and magnetic resonance confirmed the presence of the lesion and showed a pulmonary metastasis.

Conclusions: The final histopathological examination led to the diagnosis of epithelioid angiosarcoma arising in a schwannoma. The patient came to death a few months later due to a massive hemothorax. To the best of our knowledge, the present is the first case of an angiosarcoma arising in a schwannoma of the kidney.

Keywords: Kidney angiosarcoma, Epithelioid angiosarcoma, Kidney schwannoma, Angiosarcoma arising in schwannoma, Literature review

Background

Schwannoma (also known as neurilemmoma) is a benign peripheral nerve sheath tumor composed of cells with the immunophenotype and ultrastructural features of differentiated Schwann cells. It occurs in patients of any age with a slight predilection for adults [1]. The anatomic distribution is wide but the most frequent locations include subcutaneous tissues of the extremities and the head and neck region and the retroperitoneal and mediastinal soft tissues [1]. In most cases, it presents itself as a sporadic solitary lesion, but some cases are associated with the hereditary syndrome neurofibromatosis type 2 [2]. The etiology of schwannoma seems to be linked to loss of expression of the protein merlin that performs a number of critical functions such as contact-dependent inhibition of proliferation, cellular adhesion, and transmembrane signaling [3]. Diagnosis may be suspected on the basis of the clinical features of the lesion and the possible relationship with a nerve but it always requires pathological investigation. The gross appearance is that of a nodular, well-circumscribed, and encapsulated mass with a pink to yellow cut surface. Histologically, the tumor is composed of spindle cells with indistinct cell borders and moderately abundant eosinophilic cytoplasm. The most characteristic histologic feature is the nuclear palisading and the presence of eosinophilic masses circumscribed by rows of

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nuclei formerly known as Verocay bodies. There are two tissue types: Antoni A (hypercellular) and Antoni B (hypocellular with relatively abundant loose tissue). Many distinct variants of schwannoma have been described: ancient, plexiform, cellular, melanotic, microcystic, and epithelioid. By immunohistochemistry, tumor cells express S100, vimentin, calretinin, basal lamina components, and calcineurin. Schwannoma very rarely recurs after complete surgical excision, that is almost always curative, and malignant transformation is extremely rare [1]. All cases of malignant transformation reported in literature have occurred in sporadic schwannoma, and the great majority of cases consisted of a malignant peripheral nerve sheath tumor [4]. No case has been reported in patients with neurofibromatosis. The most common symptoms observed in patients with malignant change in schwannoma included pain or rapid enlargement of a pre-existing lesion. These symptoms are rare in schwannoma and should therefore support the suspicion of a malignant transformation. Sarcomas generally do not arise in peripheral nerve sheath tumors, with the exception of angiosarcoma [5]. The majority of malignant peripheral nerve sheath tumors and all the cases of angiosarcoma arising in a schwannoma have an epithelioid morphology [6]. Up to date, there is no explanation for this finding.

**Fig. 1**  
**a** Computed tomography: imaging identifies an intraparenchymal nodule in the left lung.  
**b** Computed tomography: imaging identifies the presence of a nodular mesonephric hypodense lesion characterized by post contrastographic enhancement.  
**c** Gross imaging: the kidney shows an irregular profile with granulating appearance of the hilum.  
**d** Gross imaging: sectioned tumor appears hemorrhagic, soft, and reddish.

**Fig. 2**  
**a** H&E staining (×10): numerous neoplastic vascular channels (left) that infiltrates the renal parenchyma (right).  
**b** H&E staining (×20): neoplastic cells forming vascular structures with epithelioid features and highly atypical nuclei.  
**c** H&E staining (×10): malignant cells of angiosarcoma (left) juxtaposed to benign spindle cells population of schwannoma (right).  
**d** H&E staining (×40): fine needle aspiration biopsy of the pulmonary lesion shows neoplastic cells.
Angiosarcoma is an uncommon malignant tumor presenting a recognizable vascular differentiation. It accounts for only 2 to 4% of soft tissue sarcomas [7] and occurs mainly in the adulthood and elderly, but occasional cases in children have been reported [8]. It can develop in any site but the most common locations include the skin, soft tissues, breast, bone, liver, and spleen, while the rare cases seen in children occur especially in mediastinum including the heart and pericardium. Known risk factors include previous radiation therapy and traumas, but the etiology of this neoplasm remains unknown. Recent studies have shown the role of genes involved in the receptor protein tyrosine kinase pathway, in particular the upregulation of MYC, KIT, and RET and downregulation of CDKN2C in post-radiation angiosarcomas [9]. Clinically, the symptomatology depends substantially on the location of the lesion and is related to the effect of the mass that can compress adjacent anatomical structures, to the anemia resulting from blood loss and to lymphedema; other symptoms often observed include pain, weight loss, and asthenia. The gross appearance is characterized by extensive hemorrhagic areas and infiltrating margins. Epithelioid morphology is rare in cutaneous angiosarcomas while it is frequently seen in those arising in soft tissues and visceral locations.

Regardless of the histological features, angiosarcoma is considered high grade by definition [10]; the prognosis is very poor; soft tissue forms present more than 50% of mortality within 1 year of diagnosis [11] because of the strong tendency for recurrence and the almost constant occurrence of disseminated metastases. At older ages, larger tumor size and retroperitoneal location are poor prognostic factors.

We describe a case of a complex renal lesion that consists of two components changing abruptly within the tumor: a larger, malignant neoplasm diagnosed as an epithelioid angiosarcoma and a minor benign neural tumor diagnosed as schwannoma. It is well known that angiosarcomas can develop in neurofibromas and malignant peripheral nerve sheath tumors, especially in patients with von Recklinghausen's disease. The occurrence of an angiosarcoma in a schwannoma is a very rare event as only 14 cases have been reported in the literature. To our knowledge, the present is the first case of an angiosarcoma arising in a schwannoma of the kidney.

Case presentation
A 56-year-old man with a history of non-insulin dependent diabetes mellitus was referred to the surgical

![Image](image-url)
department because of the onset of lower back pain and hematuria that occurred the previous day. The patient was not a smoker and denied alcohol consumption; his family history was unremarkable and there was no other complaint. The ultrasound of the left kidney revealed the presence of stones in the renal pelvis causing obstruction of the ureteral meatus and consequent dilatation of the upper calix. During the examination, the presence of a solid nodule with same features in the left lung, likely due to metastases (Figs. 1a-1b). A lombotomic total nephrectomy was performed, and the patient had an uneventful post-operative recovery.

Grossly, the kidney presented irregular profile due to a hilar lesion measuring 4 cm × 2.5 cm. On cut sections, it was highly hemorrhagic, soft, and reddish with infiltrating borders (Figs. 1c-1d). The tumor was extensively sampled. Microscopic examination was performed on paraffin-embedded sections stained with hematoxylin and eosin (Figs. 2 and 3). Histopathological examination showed a proliferation of canalicular structures of various sizes, sometimes with some degree of cystic changes, lined by atypical cells with epithelioid features, deeply invading the renal parenchyma and the perinephric fat. Many of these structures contained red blood cells giving the idea that it was a vascular lesion. In some fields was observed an almost solid growth pattern with erythrocytes trapped in thin spaces between neoplastic cells. Marked cellular pleomorphism, enlarged and hyperchromic nuclei, irregular nuclear contour, prominent nucleoli, and frequent mitotic figures were also evident. In the context of this lesion, few fields showed a quite different morphology consisting of spindle cells or invasive features. An immunohistochemical study was performed on formalin-fixed paraffin-embedded tissue block to define the histogenesis of the lesion. Pre-diluted antibodies produced by Ventana-Roche were used, directed against pan-cytokeratin (clone AE1/AE3/PCK26; mouse monoclonal), CD34 (clone QBEnd/10; mouse monoclonal), factor VIII (rabbit polyclonal), Ki67 (clone 30-9; mouse monoclonal), S100 (clone 4C4.9; mouse monoclonal), EMA (clone E29; mouse monoclonal), and CD10 (clone SP67; rabbit monoclonal). The malignant population was reactive for pan-cytokeratin, CD34, factor VIII, partially positive for Ki67 (positivity in about 40 % of neoplastic cells) and negative for S100, EMA and CD10, therefore was consistent with epithelioid angiosarcoma. Otherwise, the benign spindle cells population was positive for S100 and negative for Ki67 and epithelial and endothelial markers. It was so interpreted as residuals of pre-existent schwannoma. In view of these morphological and immunohistochemical findings, a diagnosis of primary renal epithelioid angiosarcoma probably arising in schwannoma was made. A CT-guided fine-needle aspiration cytology of the pulmonary lesion was subsequently performed that showed CD31-positive atypical epithelioid cells in the context of numerous erythrocytes, confirming the diagnosis of lung metastasis of angiosarcoma. During the post-operative period, the patient has not been subjected to antineoplastic therapy because of poor general health and he came to exitus a few months after diagnosis, because of a massive hemothorax caused by lung metastasis.

Conclusions

Angiosarcoma is an infrequent neoplasm with a very poor prognosis which is why it has been very rarely described in the kidney. The diagnosis of this lesion is extremely difficult if not impossible when considering just the clinical and radiological features. So, it is often referred to post-operative time, and pathological examination remains the gold standard. The occurrence of an
angiosarcoma in a pre-existent schwannoma is an exceptionally rare event with an unknown pathogenesis. In view of the rarity of the lesion, an extensive review of the literature was undertaken through a MEDLINE search using the search terms “primary renal schwannoma/primary schwannoma of the kidney,” “primary renal angiosarcoma/primary angiosarcoma of the kidney,” and “angiosarcoma arising in schwannoma.” Only reports in English have been taken into account. In Tables 1, 2, and 3 are listed the cases reported in the literature specifying the source and the clinical features of each case.

Twenty-one cases of renal schwannoma have been reported in literature (Table 1) [12–27]. Tumors involved patients ranging in age from 14 to 84 years, with a median age of 48 years and a slight predominance in females (male to female ratio of 0.75:1). Renal schwannomas were mainly located in the parenchyma and less frequently in the hilum.

Twenty-nine cases of primary renal angiosarcoma have been reported in literature [28–55]. The median age of patients was 61.5 years with an age range comprised from 24 to 86 years. The great majority of tumors have been found in males with a male to female ratio of 13.5:1 (27 males and 2 females). Angiosarcoma was seen to arise preferably in the left kidney (right to left ratio of 0.5:1). The most common symptoms reported were the classical symptoms due to a renal mass like flank pain and hematuria, while more rarely there were symptoms related to the presence of metastasis at time of diagnosis like cough, hemoptysis, and dizziness. Three cases were asymptomatic, and the lesions have been found as incidental findings during diagnostic tests conducted for other reasons.

Angiosarcomas arise very rarely in the context of a pre-existing schwannoma. To the best of our knowledge, only 14 cases have been reported in literature to date.

### Table 2: Cases of primary angiosarcoma of the kidney

| Author                  | Sex | Age (years) | Side | Year | Clinical presentation                      |
|-------------------------|-----|-------------|------|------|-------------------------------------------|
| Zhang et al. [28]       | Male | 52          | Left | 2014 | Leg pain and flank pain                   |
| Qayyum et al. [29]      | Female | 86         | Right | 2014 | Fatigue, dizziness, weight loss           |
| Liu et al. [30]         | Male | 75          | Right | 2014 | Gross hematuria                           |
| Sabharwal et al. [31]   | Male | 67          | Left  | 2013 | Flank pain, weight loss                   |
| Chaabouni et al. [32]   | Male | 59          | Right | 2013 | Flank pain, gross hematuria               |
| Singh et al. [33]       | Male | 83          | Left  | 2012 | Acute chest pain, dyspnea                 |
| Douard et al. [34]      | Male | 60          | Right | 2012 | Hodgkin’s lymphoma history                |
| Zenico et al. [35]      | Male | 56          | Left  | 2011 | Hodgkin’s lymphoma history                |
| Papadimitriou [36]      | Male | 68          | Left  | 2009 | Flank pain                                |
| Fukunaga [37]           | Male | 61          | Left  | 2009 | Hypertension                              |
| Leggio et al. [38]      | Male | 60          | Left  | 2006 | After trauma                              |
| Akkad et al. [39]       | Male | 58          | Right | 2006 | Asymptomatic                              |
| Johnson et al. [40]     | Male | 50          | Left  | 2002 | Flank pain, hemoptysis                    |
| Aksay et al. [41]       | Male | 55          | Left  | 2002 | Spontaneous rupture                       |
| Aydogdu et al. [42]     | Male | 77          | Left  | 1999 | Gross hematuria, flank pain               |
| Cerilli et al. [43]     | Male | 67          | Right | 1998 | Gross hematuria, flank pain               |
| Tsuda et al. [44]       | Male | 77          | Left  | 1997 | Gross hematuria, renal failure            |
| Mordkin et al. [45]     | Male | 75          | Left  | 1997 | Weight loss, fever                        |
| Hiratsuka et al. [46]   | Female | 59        | Right | 1997 | Hematuria                                 |
| Martinez-Piñeiro et al. [47] | Male | 66        | Left  | 1995 | Asthenia                                  |
| Kern et al. [48]        | Male | 69          | Left  | 1995 | Flank pain, hematuria, weight loss        |
| Kern et al. [48]        | Male | 56          | Left  | 1995 | Hematuria                                 |
| Adijiman et al. [49]    | Male | 36          | Right | 1990 | Flank pain, cough, hemoptysis             |
| Desai et al. [50]       | Male | 54          | Left  | 1989 | Flank pain, microhematuria                |
| Cason et al. [51]       | Male | 46          | Left  | 1987 | Flank pain, weight loss, fever            |
| Terris et al. [52]      | Male | 47          | Left  | 1986 | Flank pain                                |
| Alfred et al. [53]      | Male | 67          | Right | 1981 | Flank pain, hematuria                     |
| Askari et al. [54]      | Male | 24          | Right | 1980 | Hematuria                                 |
| Peters et al. [55]      | Male | 74          | Left  | 1974 | Weight loss                               |
[56–62]. In all these cases, an angiosarcomatous component had an epithelial morphology. Patients were aged between 17 and 74 with a median age of 55 and a male to female ratio of 1.8:1. The locations of the lesions included the neck, leg, buttock, intracranial, abdominal cavity, and inguinal region; no case has been previously reported in the kidney.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

All the authors contributed, read, and approved equally to the drafting of the manuscript. All the authors read and approved the final manuscript.

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**Table 3** Cases of angiosarcoma arising in schwannoma

| Author                        | Sex   | Age (years) | Location                | Year |
|-------------------------------|-------|-------------|-------------------------|------|
| Mahajan et al. [56]           | Male  | 41          | Neck, vagus nerve       | 2014 |
| Li et al. [57]                | Male  | 67          | Right abdominal adrenergic nerve | 2012 |
| Li et al. [57]                | Male  | 38          | Right inguinal sciatic nerve | 2012 |
| Li et al. [57]                | Male  | 55          | Left neck, vagus nerve  | 2012 |
| Lee et al. [58]               | Male  | 73          | Left thigh, sciatic nerve | 2007 |
| Ito et al. [59]               | Male  | 66          | Intracranial vestibular nerve | 2007 |
| McMenamin et al. [60]         | Female| 74          | Right neck, vagus nerve | 2001 |
| McMenamin et al. [60]         | Female| 40          | Right thigh, sciatic nerve | 2001 |
| McMenamin et al. [60]         | Female| 17          | Right neck, phrenic nerve | 2001 |
| McMenamin et al. [60]         | Female| 39          | Right buttoc            | 2000 |
| Ruckert et al. [61]           | Male  | 50          | Right neck, vagus nerve | 1999 |
| Mentzel et al.                | Female| 73          | Right neck, vagus nerve | 1999 |
| Mentzel et al.                | Male  | 63          | Right neck, vagus nerve | 1999 |
| Trassard et al. [62]          | Male  | 65          | Right thigh, sciatic nerve | 1996 |

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