Clinical and pathologic features of primary angiosarcoma of the kidney

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Abstract

Purpose of review

Primary angiosarcoma of the kidney is extremely rare; hence relatively little is known regarding its clinicopathologic features and prognosis. Herein, we review the literature on primary renal angiosarcoma with emphasis on the clinical and pathologic features.

Recent findings

Approximately 64 cases have been reported in the literature and most cases occur in the 6^{th} - 7^{th} decade with a strong male predominance. The aetiology is unknown. Patients present with flank pain, haematuria, abdominal mass and weight loss. A considerable number of patients develop metastatic disease at diagnosis or shortly afterwards. Grossly, the tumour comprises ill-defined haemorrhagic spongy masses often with necrosis. Microscopically, the tumour is composed of anastomosing capillary-sized vessels which are lined by malignant endothelial cells. The mainstay of treatment is surgery followed by radiation therapy with or without chemotherapy.

Summary

Renal angiosarcomas are highly aggressive tumours with dismal outcome; and they must be distinguished from morphologically similar lesions of the kidney.

Keywords: Renal angiosarcoma; Renal hemangiosarcoma; Renal haemangioma.

Introduction

Angiosarcoma is a malignant neoplasm of endothelial cells. It accounts for <2% of soft tissue sarcomas [1, 2]. About a third arise in the soft tissue, one-third in the skin and one-third in other anatomical sites including the breast, bone and liver [1, 3, 4]. Primary renal angiosarcoma, also referred to as renal hemangiosarcoma is an extremely rare neoplasm. To date, approximately 64 primary renal angiosarcomas have been described in the literature, mostly in the form of individual case reports and small series [1 - 17]. The largest series contained eight cases [4]. We present a review of the clinical and pathologic features of primary renal angiosarcoma, to better understand this rare neoplasm.

Epidemiology

There is a wide age range however, most cases occur in the 6^{th} and 7^{th} decade. The mean age at diagnosis is 61 years (range 24 to 95) [1 - 17]. The tumour predominantly affects men with a male-female ratio of 7:1 [1].

Aetiology

The aetiology is unknown. Androgen may play a role because the tumour predominantly occurs in men; however, there is no conclusive evidence for this [18, 19]. One case report describes the occurrence of renal angiosarcoma in two brothers; however, no hereditary or common predisposing factor was identified [15]. Although there are no known specific risk factors for primary renal angiosarcoma, angiosarcomas arising in other anatomical sites have been associated with predisposing factors, including exposure to polyvinyl chloride, radiation, arsenic, thorotrast and chronic lymphedema [1, 4]. A subset of cases is associated with a variety of syndromes, such as Maffucci, Klippel-Trenaunay, Bilateral retinoblastoma, Ollier's disease, Xeroderma pigmentosum and Neurofibromatosis [10, 20].

Clinical features

Patients are frequently symptomatic, and the most common presentation is flank pain. Few cases are discovered incidentally during routine investigations [10, 16, 17]. Other clinical features include haematuria, abdominal mass, weight loss, fatigue, dizziness, fever and malaise [1- 17]. Rarely, patients may present with spontaneous rupture of the tumour resulting in retroperitoneal hematoma [11]. Renal angiosarcoma may co-exist with other tumours including minute clear cell carcinomas [14] and adult Wilms tumour [21].

Metastasis is a common feature and a considerable number of patients (69.4%)develop metastatic disease at diagnosis or shortly afterwards [1, 18]. The lungs and liver are the most common sites of metastasis. Other sites include the peritoneum, bone, chest wall, spleen, skin, soft tissue and lymph nodes. Metastasis commonly involves two or more sites [1, 18].

Imaging

Pre-operative distinction between malignant lesions of the kidney is a well-known radiographic diagnostic challenge. The tumour appears as a hypodense mass with variable peripheral enhancement on CT [1, 12, 22]. There are no specific imaging findings for angiosarcoma, hence the

difficulty in distinguishing between angiosarcoma and renal cell carcinoma. Renal cell carcinoma can be vascular and both tumours may present as large necrotic renal masses [1, 3, 4, 12]. However, CT imaging is extremely useful in disease staging. CT findings of multiple small lesions in the lungs and liver, at the same time with a single large renal mass, should raise clinical suspicion of metastasis from a renal primary [1, 4].

Pathology

Grossly, the tumour consists of ill-defined haemorrhagic spongy masses often with necrosis. Tumours are usually large ranging from 3.7 to 30cm in maximum dimension (Mean, 13cm) [1, 4, 19]. Replacement of the renal parenchyma with extension into perirenal soft tissue is a common feature [2]. Renal angiosarcoma shares similar morphology with angiosarcomas arising elsewhere [1, 4, 19].

The morphological features are diverse and can vary both within and between cases, ranging from well-formed tumours composed of anastomosing capillary-sized vessels to poorly formed tumours composed of solid sheets of malignant epithelioid and spindled cells, with a hint of vasoformation. In most tumours spindled cells predominate; in few, epithelioid cells may be predominant; and such tumours are classified as epithelioid angiosarcomas [1, 3, 4, 13, 18].

Microscopically, the anastomosing vascular channels or capillary-sized vessels are lined by malignant endothelial cells. The spindled andepithelioid tumour cells are pleomorphic with hyperchromatic nuclei, irregular nuclear outlines and coarse chromatin distribution. The malignant endothelial cells exhibit multilayering and papillary tufting. Tumours may show foci of coagulative necrosis, extensive haemorrhage and significant mitotic activity [1-17, 19]. A diffusely infiltrative growth pattern with variable invasion of perinephric fat and perirenal soft tissue may be confirmed on histology [1, 4, 19]. Poorly-vasoformative angiosarcoma with solid sheets of bizarre looking malignant endothelial cells, usually with epithelioid morphology closely mimics carcinoma on histology. This is a recognized pitfall in diagnosis and a panel of antibodies may be required to distinguish angiosarcoma from other morphologic mimics [19, 23].

Immunohistochemically, angiosarcomas are positive for at least one endothelial cell marker (CD34, CD31, ERG, FLI1 and Factor VIII related antigen) [1-4]and It is good practice to include at least two endothelial markers in the panel of antibodies. Tumour cells are typically negative for cytokeratin except for epithelioid angiosarcomas which may stain positive for cytokeratin [13, 23]. HHV-8, a marker for Kaposi sarcoma is typically negative.

Genetics

There is keen interest to discover genetic drivers of angiosarcoma and how that might be used as targets of new therapy. Expression profiling studies indicate that angiosarcomas in general show distinct up-regulation of vascular–specific receptor tyrosine kinases, including FLT1 (also known as VEGFR1), TIE1, TEK, SNRK and KDR (also known as VEGFR2) [24]. A subset of cases (10%) harbours KDR mutation which correlates with strong and diffuse expression of KDR protein either by immunohistochemistry or immunofluorescence; and are restricted to the breast regardless of exposure to radiation [24]. Angiosarcomas also show overexpression of HIF-1α and HIF-2α which are upstream regulators of VEGF [25]

Furthermore, consistent high level MYC gene amplification by FISH is seen in radiation induced and chronic lymphedema associated angiosarcoma, but not in radiation-induced atypical vascular lesions or other subgroups of angiosarcoma [26].

Whole-genome, whole-exome and targeted sequencing studies suggest that angiosarcomas harbour recurrent PTPRB (a negative regulator of vascular growth factor tyrosine kinases) and PLCG1 (a signal transducer of tyrosine kinase) mutations [27]. Both genes are involved in angiogenesis and this reinforces current efforts to target angiogenesis signaling in angiosarcomas [27]. None of these mutations have been reported in renal angiosarcomas.

Treatment

Early diagnosis and prompt referral to specialist sarcoma services remain an important goal in the management of soft tissue and visceral sarcomas [28, 29]. It is recommended that all patients should be managed by a specialist sarcoma multidisciplinary team (MDT)composed of pathologists, surgeons, medical oncologists, clinical oncologists, radiologists, nurses and allied health professionals. The MDT team makes decisions about the best line of management on a case by case basis according to treatment guidelines [28, 29]. Although treatment guidelines exist in general for soft tissue angiosarcoma, none are currently available for the management of renal angiosarcoma leading to varying treatments. The lack of specific treatment guidelines may be due to the rarity of the tumour [1, 4, 18].

Surgery is the mainstay of treatment followed by radiation therapy and chemotherapy in localized and metastatic disease respectively [1, 18, 20]. In Mark's series, the 5-year actuarial disease-free survival (DFS) was 43% in patients treated with surgery and radiotherapy, with or without chemotherapy compared with 17% for patients who underwent surgery with or without chemotherapy ($p=0.03$) [30]. In Pawlik's series of cutaneous angiosarcoma, patients who received adjuvant radiotherapy had a median survival that was 4 times longer compared with patients who did not (36.1months vs. 9.2months) [31]. Two case reports describe the use of adjuvant targeted therapies for renal angiosarcoma. One case was treated with recombinant interleukin- 2 therapy and the other, with chemotherapy (oxaliplatin and paclitaxel) and bevacizumab. However, despite treatment, both patients died of disease within 13 months [32, 33]. Adjuvant therapies have met with limited success, and patients may develop progressive disease and metastasis regardless of treatment [33].

Differential diagnosis

Anastomosing renal haemangioma shows considerable clinical and morphologic overlap with renal angiosarcomas. They share similar clinical features including flank pain, hematuria and abdominal mass; exhibit similar anastomosing pattern on morphology; and are positive for markers of endothelial differentiation on immunohistochemistry [4, 34, 35]. It is however important to distinguish between both tumours because of the implications on management and prognosis. Renal haemangiomas small tumours composed of anastomosing capillary-sized vascular channels lined by cytologically bland hobnail endothelial cells, separated by moderate amount of stroma with non-endothelial supporting cells. [4, 34]. They lack atypical features such as hyperchromatic nuclei, irregular nuclear outline, multilayering, atypical mitotic figures and necrosis. Although cases with tumour infiltration of segmental branches of the renal vein and perinephric fat have been reported,

renal haemangiomas are considered benign [34, 35]. In contrast to renal angiosarcoma, anastomosing renal haemangioma runs a benign course without evidence of disease recurrence during follow up [34, 35].

Sarcomatoid renal cell carcinoma is not a distinct histological entity or subtype of renal cell carcinoma. It represents renal cell carcinoma of any type exhibiting a sarcomatoid differentiation, including clear cell renal cell carcinoma, chromophobe renal cell carcinoma, papillary renal cell carcinoma etc. Characteristically, the tumour contains both epithelial and sarcomatoid elements and the presence of sarcomatoid change confers a poor prognosis [36].

Haemorrhagic renal cell carcinoma is another diagnostic consideration because it may mimic renal angiosarcoma on imaging as indicated previously; however, distinction can be made on histologic assessment and immunohistochemistry.

Prognosis

Of 64 cases of primary renal angiosarcoma reported in the literature, outcome data was available in 47 cases (73%). The mean follow-up was 8.6 months (range, 1 - 30). Seventy-seven percent (36 cases) of patients died of disease at a mean interval of 7.3 months (range, 1-24); 6% (3 cases) died from unrelated causes (one from heart failure and two from sepsis); 9% (4 cases) of patients had no evidence of disease at a mean interval of 21 months (range, 6 – 30); 4% (2 cases) were alive with disease at a mean interval of 12 months; and two patients (4%) were reported alive and well, but it is not clear if they had evidence of disease or not (Table 1).

The prognosis of renal angiosarcoma is poor, with high rates of tumour related deaths. Local recurrence and distant metastasis commonly occurs [1, 18]. Patients with metastatic disease have more than a threefold increase in the risk of death compared to patients without metastatic disease (hazard ratio: 3.27, 95% CI, 1.48–7.24; p=0.004) [18]. Patients without metastasis have a median disease-free survival (DFS) of 6 months [18].

The dismal outcome in renal angiosarcoma is comparable to angiosarcomas arising in other anatomical sites. Lahat et al in a series of 222 patients reported a median survival and 5-year disease-specific survival (DSS) rate of 10 months (range, 1-69) and 16% respectively for patients with metastatic disease compared with 49 months (range, 1-188) and 44% respectively for patients with localised disease [37].

Poor prognostic factors for angiosarcomas in general include large tumour size (with a threshold of 5cm) [30, 37, 38], high tumour grade, head and neck location [18, 30], margin status, epithelioid histologic component [37], retroperitoneal location, older patient age, and higher Ki67 values (≥ 10%) [38]. As noted by Lahat et al, of the several factors identified on univariate analysis with significant prognostic import on disease specific survival, tumour size (>5cm vs ≥5cm, p=0.01) and epithelioid histologic component (p=0.008) remained significant in the multivariate analysis as independent prognostic factors [37]. Tumours > 5cm have a 5-year survival of 13% compared with a 5-year survival of 32% for tumours <5cm [30].

Conclusion

We conclude that primary renal angiosarcomas are highly aggressive tumours with a dismal outcome; and they must be distinguished from morphologically similar lesions of the kidney. They should be considered as a differential diagnosis of large necrotic renal masses on imaging. Definitive diagnosis of primary renal angiosarcoma requires histological assessment. It is recommended that all cases should be managed by a specialist multidisciplinary team with experience and expertise in sarcoma. The poor clinical outcome despite conventional therapy, indicates that there remains a pressing need for further research into molecular and genetic drivers of angiosarcoma that might help in the design of novel targeted therapies.

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Papers of interest, published recently have been highlighted as:

.. Of major importance

1...Omiyale AO. Clinicopathological features of primary angiosarcoma of the kidney: a review of 62 cases. Transl Androl Urol 2015; 4: 464-73. **Comprehensive review of primary renal angiosarcoma.**

2.Chaabouni A, Rebai N, Chabchoub K, Foratid M, Bouacida M, Slimen MH, et al. Primary renal angiosarcoma: case report and literature review. Can Urol Assoc J 2013;7: E430-2.

3. Singh C, Xie L, Schmechel SC, Manivel JC, Pambuccian SE. Epithelioid angiosarcoma of the kidney: a diagnostic dilemma in fine-needle aspiration cytology. Diagn Cytopathol 2012; 40 Suppl 2: E131-9

4. Brown JG, Folpe AL, Rao P, Lazar AJ, Paner GP, Gupta R, et al. Primary vascular tumours and tumor-like lesions of the kidney: a clinicopathologic analysis of 25 cases. Am J Surg Pathol 2010; 34:942-9

5. Prince CL. Primary angio-endothelioma of the kidney: report of a case and brief review. J Urol 1942; 47:787-9

6. Juan CJ, Yu CH, Hsu HH, Chian CP, Huang GS, Fan HC, et al. Visceral and non-visceral angiosarcoma: Imaging features and clinical correlation. Chin J Radiol 2000; 25:183-9

7. Testa G, Talamona G, Tufano A, Marino-Marsilia G. Primary renal angiosarcoma: a case report. Acta Urologica Italica 1998; 12:225-7.

8. Xuan Y. Primary renal angiosarcoma: one case report and literature review. Chin J Clin Oncol 2008; 5:229-30.

9. Sesar P, Ulamec M, Šoša D, Trnski D, Tomas D. Primary renal angiosarcoma. Acta Clin Croat 2012; 51:182.

10. Zenico T, Saccomanni M, Salomone U, Bercovich E. Primary renal angiosarcoma: case report and review of world literature. Tumori 2011; 97: e6-e9.

11. Aksoy Y, Gürsan N, Ozbey I. Spontaneous rupture of a renal angiosarcoma. Urol Int 2002; 68:60-2.

12. Detorakis EE, Chryssou E, Raissaki M, Androulidakis E. Heretis I, Haniotis V, Karantanas A. Primary renal angiosarcoma: radiologic-pathologic correlation and literature review. Tumori 2013; 99: e111-6.

13. Liu H, Huang X, Chen H, Wang X, Chen L. Epithelioid angiosarcoma of the kidney: a case report and literature review. Oncol lett 2014; 8:1155-8.

14. Fukunaga M. Angiosarcoma of the kidney with minute clear cell carcinomas: a case report. Pathol Res Pract 2009; 205:347-51.

15. Kern SB, Gott L, Faulkner J, 2nd. Occurrence of primary renal angiosarcoma in brothers. Arch Pathol Lab Med 1995; 119:75-8.

16. Akkad T, Tsankov A, Pelzer A, Peschel R, Bartsch G, Steiner H. Early diagnosis and straightforward surgery of an asymptomatic primary angiosarcoma of the kidney led to long-term survival. Int J Urol 2006; 13:1112-4

17. Yamamoto Y, Izaki H, Harada A, Taue R, Kishimoto T, Tanimoto S, et al. A case of renal capsular hemangiosarcoma. Hinyokika Kiyo 2006; 52:215-7.

18... Lacovelli R, Orlando V, Palazzo A, Cortesi E. Clinical and pathological features of primary renal angiosarcoma. Can Urol Assoc J 2014; 8(3-4): E223-E226. **Recent review of primary renal angiosarcoma.**

19. Eble, JN, Sauter G, Epstein JI, Sesterhenn IA. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. IARC Press, Lyon, France; 2004

20. Penel N, Marréaud S, Robin YM, Hohenberger P. Angiosarcoma: state of the art and perspectives. Crit Rev Oncol Hematol 2011; 80:257-63

21. Yau T, Leong CH, Chan WK, Chan JK, Liang RHS, Epstein RJ. A case of mixed adult Wilms' tumour and angiosarcoma responsive to carboplatin, etoposide and vincristine (CEO). Cancer Chemother Pharmacol 2008; 61:717-20.

22. Sabharwal S, John NT, Kumar RM, Kekre NS. Primary renal angiosarcoma. Indian J Urol 2013; 29:145-7.

23. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F (4thEds): World Health Organization Classification of Tumours of Soft tissue and Bone. IARC: Lyon 2013.

24. Antonescu CR, Yoshida A, Guo T, Chang NE, Zhang L, Agaram NP, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase Inhibitors. Cancer res 2009; 69:7175-9.

25. Rathmell WK, Acs G, Simon MC, Vaughn DJ. HIF transcription factor expression and induction of hypoxic response genes in a retroperitoneal angiosarcoma. Anticancer Res 2004; 24:167–169.

26. Guo T, Zhang L, Chang NE, Singer S, Maki RG, Antonescu CR. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Genes Chromosomes Cancer 2011; 50: 25-33.

27**..** Behjati S, Tarpey PS, Sheldon H, Martincorena I, Loo PV, Gundem G, et al. Recurrent PTPRB and PLCG1 mutations in angiosarcoma. Nature Genetics 2014; 46; 376-379. **Study identified novel recurrent mutations in angiogenesis signalling genes in angiosarcoma**

28. Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas Clin Sarcoma Res 2016; 6:20.

29. ESMO/European Sarcoma Network Working Group: Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up Ann Oncol, 25 (Suppl 3) (2014), pp. iii102-iii112.

30. Mark RJ, Poen JC, Tran LM, Fu YS, Julliard GF. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer 1996; 77: 2400–6.

31. Pawlik TM, Paulino AF, McGinn CJ, Baker LH, Cohen DS, Morris JS, Rees R, Sondak VK. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer 2003; 98: 1716-26.

32. Yoshida K, Ito F, Nakazawa H, Maeda Y, Tomoe H, Aiba M. A case of primary renal angiosarcoma. Rare tumors 2009; 1: e28.

33. Celebi F, Pilanci KN, Saglam S, Balci NC. Primary renal Angiosarcoma with progressive clinical course despite surgical and adjuvant treatment: a case report. Oncol Lett 2015; 9: 1937-9.

34. Omiyale AO. Anastomosing haemangioma of the kidney: A literature review of a rare morphological variant of haemangioma. Ann Transl Med. 2015; 3:151.

35. Omiyale AO, Golash A, Mann A, Kyriakidis D, Kalyanasundaram K. Anastomosing haemangioma of the kidney involving a segmental branch of the renal vein. Case Rep Surg. 2015; 2015: 927286.

36. Viswanathan S, Desai SB, Prabhu SR, Amin MB. Squamous differentiation in a sarcomatoid chromophobe renal cell carcinoma: an unusual case report with review of the literature. Arch Pathol Lab Med 2008;132: 1672 - 4.

37. Lahat G, Dhuka AR, Hallevi H, Xiao L, Zou C, Smith KD, et al Angiosarcoma clinical and molecular insights. Ann Surg 2010; 251: 1098 -106.

38. Meis-Kindblom, J. and Kindblom, L.G. Angiosarcoma of soft tissue: a study of 80 cases. Am J Surg Pathol. 1998; 22: 683–97.