BMC Urology

CASE REPORT

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Primary pure angiosarcoma of the testis: a vanishingly rare malignancy. Case report and literature review

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Abstract

Background: Primary pure angiosarcoma of the testis is an exceptionally rare testicular malignancy, which is poorly understood. We present the fifth and youngest case in the current medical literature. Additionally, all cases of angiosarcoma of the testicle, both occurring with associated germ cell tumour and without, were compared in an extended tabular format.

Case presentation: A 56-year old man presented with unilateral scrotal pain, swelling and erythema. Ultrasonography revealed two testicular lesions with a high suspicion of malignancy but serum tumour markers were negative. A radical orchidectomy was performed with clear surgical margins. Diagnosis of primary pure angiosarcoma of the testis was confirmed on subsequent histopathology.

Conclusions: Primary pure angiosarcoma is a rare testicular neoplasm. We present the fifth case in the literature. Clinical and radiological features are non-specific. The diagnosis is purely histological, with the pathologist choosing immunohistochemistry based on abnormal morphology. Local invasiveness is variable but metastatic sites are typical for extra-gonadal angiosarcomas. Primary pure testicular angiosarcoma diagnosis confers a relatively better prognosis compared to angiosarcoma arising in the context of a testicular germ cell tumour. While extra-gonadal angiosarcomas are associated with high rates of local recurrence following resection, in all cases of testicular angiosarcoma there were no local recurrences following radical orchidectomy. Surgical resection remains the most effective treatment for both subtypes of testicular angiosarcoma.

Keyword: Angiosarcoma, Testicular malignancy, Immunohistochemistry, Cisplatin, Radiotherapy, Embryonal carcinoma

Background

Angiosarcomas are an uncommon group of malignancies that arise from vascular endothelial cells and generally carry a poor prognosis. Reported five-year survival rate is 35% in non-metastatic disease [1]. Incidence is highest in the sixth and seventh decades of life, although angiosarcoma can develop at any age [2]. Aetiological factors known to give rise to angiosarcoma include radio- or chemotherapy, vinyl chloride, arsenic and thorium dioxide [2, 3]. These malignancies behave aggressively, with extensive local invasion, early and widespread metastases and high rates of local recurrence following resection [2, 3]. Metastasis is thought to occur via haematogenous spread [4]. The most frequent sites of metastasis are the lungs, liver, bones and lymph nodes [4]. In most cases of angiosarcoma, extensive metastatic disease is present at the time of diagnosis [4]. Surgical resection, where possible, comprises the mainstay of treatment. Angiosarcomas are relatively unresponsive to chemotherapy and

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radiotherapy [5–7]. Angiosarcoma arising as a primary malignancy in the testis (PPAS) is extremely rare.

Germ cell tumours (GCT) are the most common testicular neoplasm, which most frequently comprises teratoma or seminoma [8, 9]. GCTs affect young men, the majority of cases occur between the ages of 20–39 years [10, 11]. Two to four percent of teratomatous elements within GCTs undergo malignant transformation [6, 12, 13], and sarcomatous transformation predominates over carcinoma [7, 14]. Transformation of testicular GCT to angiosarcoma is extremely rare, with eight cases reported in the literature to date. Once angiosarcoma arises, it can metastasise with, or independently, of other tumour cell types and its behaviour is usually aggressive [15].

For the purposes of this paper, the following subtypes of angiosarcoma are henceforth referred to as: extra-testicular soft tissue angiosarcomas (extra-gonadal), and two gonadal subtypes: primary pure angiosarcoma of the testis (PPAS), and angiosarcoma as a component of a testicular germ cell tumour (AS-GCT). In the latter, the angiosarcoma component might arise either within the testicular primary or within a germ cell tumour metastasis.

PPAS and AS-GCT are extremely rare, thus little is known about these conditions and further work is required. Here, we describe the fifth and youngest case of PPAS. Following, we summarise all previous cases of PPAS [16–19] and AS-GCT [7, 13, 15, 20–23] via an extended tabular approach.

Case presentation

We report our case of a 56-year-old man of Bulgarian origin working in the UK, who initially presented to primary care with a four-day history of right scrotal swelling, redness and pain, with a palpable abnormal testicular mass on examination. The patient had no past medical or family history of note. He was a 30-pack year smoker, with no occupational exposure, nor any history of previous chemo- or radio-therapy. He was treated with oral antibiotics for presumptive clinical diagnosis of epididymo-orchitis and an urgent ultrasound scan was arranged in secondary care. All blood tests were normal, including a full blood count and differential, urea and electrolytes, β-HCG, lactate dehydrogenase (LDH), and alpha-fetoprotein (AFP).

Ultrasonography demonstrated two discrete, heterogenous, hypoechoic lesions within the parenchyma of the right testis, with some cystic changes. The larger lesion measured 2 cm in diameter. There was no evidence of extension beyond the testicular tunica albuginea. Angiosarcomas typically appear highly vascular on ultrasonography, however in this case was there was no evidence of internal vascularity (Fig. 1a). Bilateral simple epididymal cysts were noted, as well as a small volume hydrocele of the left testis.

In the context of partially treated epididymo-orchitis, our differential diagnoses at that time included intra-testicular abscess and primary testicular neoplasm, potentially a teratoma. The case was discussed at local multi-disciplinary team (MDT) meeting and a right radical orchidectomy as a definitive therapeutic procedure was performed.

Pathological examination revealed the right testis to measure $50 \times 40 \times 40$ mm (average male $50 \times 20 \times 30$ mm), and the spermatic cord measured $45 \times 20 \times 25$ mm. This gives an estimated testicular volume of 41.6 ml, where a normal range is 12–30 ml [24]. On gross inspection, two discrete, adjacent lesions distorted the testicular parenchyma. The first lesion was a cream-coloured tumour that measured $17 \times 19 \times 17$ mm. The second lesion comprised an irregular haemorrhagic area with an ill-defined edge that measured $20 \times 20 \times 20$ mm. The surrounding parenchyma appeared macroscopically normal. Neither lesion appeared to infiltrate the tunica or hilum.

Microscopically, both lesions displayed similar appearances (Fig. 1b–e). Each comprised sheets of cells, mainly with a lace-like pattern of infiltration, although in places solid sheets of cells were visualised. The cells exhibited markedly pleomorphic nuclei with prominent nucleoli. The cytoplasm contained eosinophilic granules of variable sizes. Large areas of haemorrhage and focal necrosis were noted. Separate to these nodules, tumour was noted to infiltrate between seminiferous tubules (Fig. 1c) and into the stroma of the rete testis, but not into the hilum. Resected surgical margins were negative.

Immunohistochemical analysis was performed. The lesions were diffusely and strongly positive for vascular markers, CD31 and CD34. The markers looking for potential background germ cell tumour (AFP, Oct3/4, Glypican 3, Beta-HCG, CD30 and CD117) were negative. The following antibodies were also negative: EMA, S100, CAM5.2, MNF116, BerEp4 and calretinin.

In light of these findings, the final histopathological diagnosis was given as high-grade angiosarcoma ie PPAS. The patient had a re-staging CT scan three months post operatively due to lower back pain, which demonstrated no evidence of recurrence or metastatic disease. Subsequent follow up continued with active surveillance at a tertiary centre. The patient remained well at review six months after initial presentation.

Discussion and conclusions

We have reported the fifth case of primary pure angiosarcoma (PPAS) of the testis. The four existing cases of PPAS, plus the index case, are summarised in Tables 1

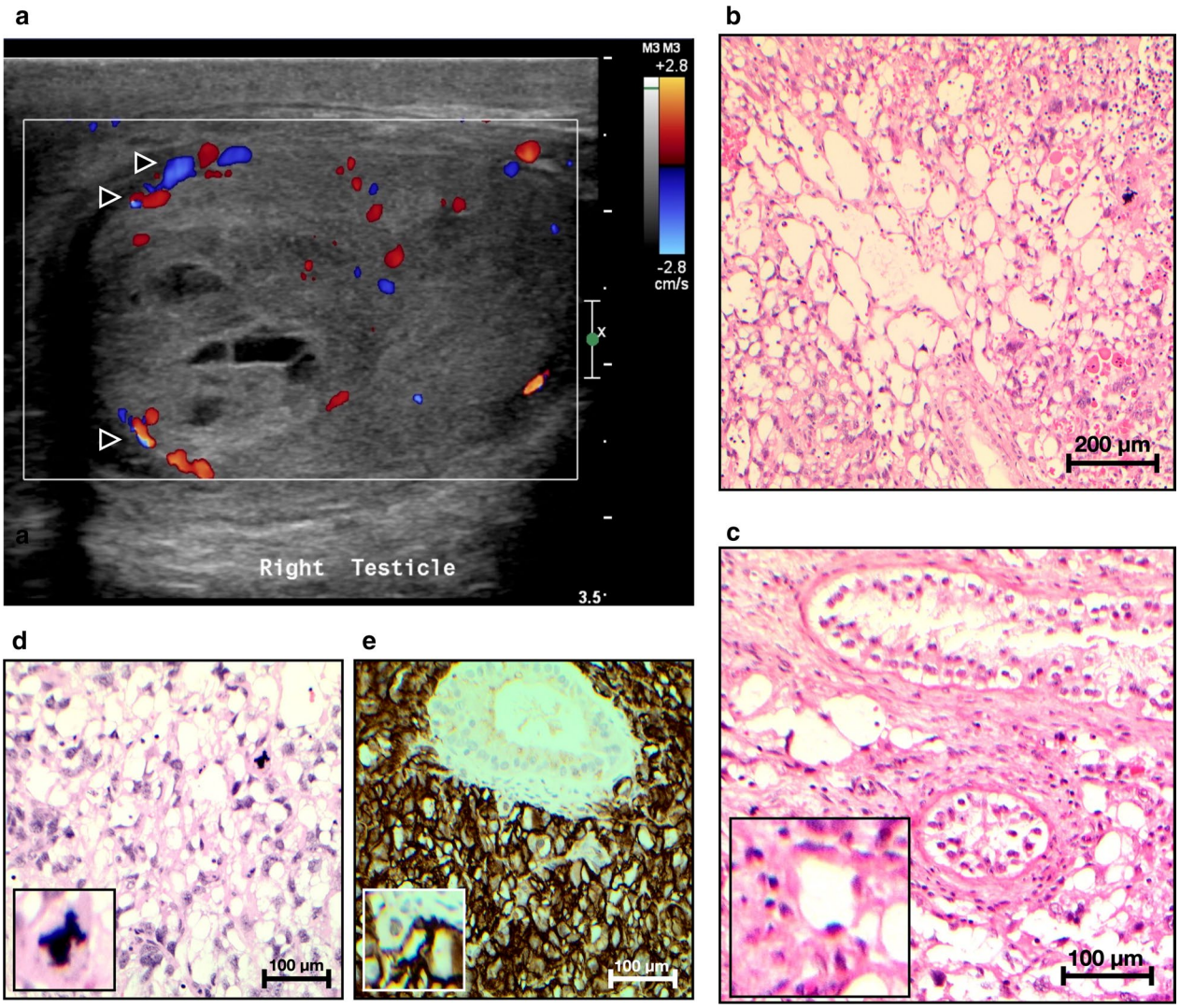

Fig. 1 Micro- and Macroscopic appearance of this case of PPAS. **a** Doppler ultrasound scan of the patient's right testicle, demonstrating one of the suspicious lesions (white square), with areas of vascularity that surrounds the lesion but not evident within it (black arrowheads with white border). **b** Hematoxylin and eosin stain of primary testicular AS at 10 × magnification. **c** Hematoxylin and eosin stain of PPAS at 20 × magnification, demonstrating a seminiferous tubule and several malignant cells infiltrating in and around the tubules. **d** Hematoxylin and eosin stain of PPAS at 20 × magnification, demonstrating markedly atypical, plump endothelial cells with atypical mitoses. **e** CD31 staining at 20 × magnification, demonstrating strong and diffuse CD31 immunopositivity

and 2 [16–19]. The eight previous cases of AS-GCT are summarised in Tables 3 and 4 [7, 13, 15, 20–23].

PPAS tends to occur in elderly patients (median 63 years, 56–80, $n=5$), whereas AS-GCT affects younger men (median 27 years, 16–38, $n=8$). The aetiology of all four previous cases of PPAS, plus the index case presented, remains unknown. Previous radiation therapy and chemotherapy are known causative factors in the pathogenesis of extra-gonadal angiosarcomas [2, 3]. Indeed, angiosarcoma first developed in three of the eight cases of AS-GCT following the use of platinum-based chemotherapy regimens and/or radiotherapy to treat primary testicular germ cell tumours. It has been hypothesised that these systemic therapies might have triggered clonal progression to angiosarcoma as well as hastening metastasic disease due to selective eradication of less aggressive germ cell tumour cell types [5, 7, 13, 21]. However, while some of the testicular primaries were extensively sampled, it is possible that components of angiosarcoma had already been present within the primary germ cell tumours prior to systemic treatment, but were missed. In contrast, the remaining five cases of

Table 1 Clinical and pathological features of all known cases of PPAS

Case	Age (years)	Diagnosis	Presentation		Investigations		Macroscopic features of testicular lesion		
			Symptoms (duration)	Patient noticed lump? (duration)	Bloods	Testicular ultrasound	Site	Appearance	Size (mm)
Current case	56	PPAS	Testicular pain, swelling, redness (4 days)	No	Normal	Two lesions Heterogenous, hypoechoic, some cysts, no vascularity	Parenchyma, rete testis, tunica	*A:* cream-coloured, Solid *B:* Haemorrhagic, infiltrative	*A:* 17 × 17 × 19 *B:* 20 × 20 × 20
Piotrowski et al. [19]	58	PPAS	Hip pain, back pain (3 months)	No	Normal	Two lesions	*A:* Parenchyma, epididymis *B:* Spermatic cord	*N/A*	*A:* 120 × 68 × 68 *B:* 35 × 24 × 20
Jain et al. [18]	63	PPAS	Testicular enlargement (8 months), preceding testicular firmness (10 years)	Yes (10 years)	Normal	Solid lesion	Parenchyma replaced by tumour	Haemorrhagic, necrotic, focal solid white	110 × 80 × 70
Armah et al. [17]	80	PPAS	Painless lump (2 months), hydrocoele (7 years)	Yes (2 months)	*N/A*	*N/A*	Parenchyma, epididymis	Haemorrhagic, solid	30
Mašera et al. [16]	74	PPAS, epithelioid	Fever unknown cause (3 weeks)	No	CRP↑ ESR↑	Transonic, vascularity	Parenchyma	Haemorrhagic, brown-white, infiltrative	17

Table 2 Therapeutic strategies and outcomes for all known cases of PPAS

Case	Testicular lesion		Metastases	Outcome
	Treatment (margins)	Local recurrence		
Current case	Orchidectomy (clear)	No	No	Alive and well after 6 months
Piotrowski et al. [19]			*At presentation:* Bones, lungs, right retroperitoneum, right pelvic LN's	Died after 6 months
Jain et al. [18]			*3 months after presentation:* Widespread bones	Died after 3 months
Armah et al. [17]			No	Alive and well after 20 months
Mašera et al. [16],			No	Died after 1 month from stroke

AS-GCT did not occur in association with any known risk factor for extra-gonadal angiosarcoma [15, 20, 22, 23]. Angiosarcoma was identified as a component of teratomatous germ cell tumours prior to the administration of systemic therapies. In these cases, the angiosarcoma components were postulated to occur as a consequence of malignant transformation within teratomatous foci [15, 20, 22, 23].

In comparison, none of the four previous cases of PPAS, nor the index case, were exposed to any identifiable risk factor for angiosarcoma. Malignant transformation of a teratoma is unlikely to explain the pathogenesis of PPAS, because no teratomatous components were identified on microscopic or

Table 3 Clinical and pathological features of all known cases of AS-GCT

Case	Age (years)	Diagnosis	Presentation		Testicular lesion				
			Symptoms (duration)	Bloods	Diagnosis	Site	Size (mm)	Definitive treatment (margins)	Local recurrence
Primary angiosarcoma in germ cell tumour									
Malagón et al. [15]	25	AS-GCT	*N/A*	*N/A*	Teratoma, yolk sac tumour, angiosarcoma	*N/A*	*N/A*	Orchidectomy (*N/A*)	*N/A*
Malagón et al. [15],	35	AS-GCT	*N/A*	*N/A*	Teratoma, yolk sac tumour	*N/A*	*N/A*	Orchidectomy (*N/A*)	*N/A*
Sahoo et al., [23]	23	AS-GCT, epithelioid	Right flank pain, back pain	Normal	Teratoma	Parenchyma	65 × 60 × 55	Orchidectomy (clear)	No
Steele et al. [22]	24	AS-GCT, epithelioid	Left testis mass (6 months)	Normal	Teratoma, epithelioid angiosarcoma	Parenchyma, rete testis, epididymis, spermatic cord	80 × 70	Orchidectomy (clear)	No
Hughes et al. [20]	16	AS-GCT	Right testis mass (1 months)	Normal	Teratoma, angiosarcoma	Parenchyma	90 × 70 × 65	Orchidectomy (clear) post-op RT	No
Therapy-related angiosarcoma in germ cell tumour									
Idrees et al. [7]	38	AS-GCT	Abdominal pain	AFP 8320	Teratoma, yolk sac tumour, seminoma	Parenchyma, epididymis, para-testicular soft tissue	*N/A*	Orchidectomy (clear)	No
Lee et al. [21]	35	AS-GCT, epithelioid	*N/A*	*N/A*	Seminoma	*N/A*	80	Orchidectomy (clear)	No
Ulbright et al. [6]	17	AS-GCT	Testis mass, back pain (1 years)	*N/A*	Teratoma	*N/A*	*N/A*	Orchidectomy (*N/A*)	No

immunohistochemical evaluation of any case. Furthermore, malignant teratomas seldom occur in the elderly [25]. Therefore, the etiology of PPAS remains unclear.

Clinical and radiological features prior to definitive surgery (radical orchidectomy) are *not* diagnostic of PPAS [20, 22, 23]. On ultrasonography, the index case did not display the internal vascularity that is regarded as a characteristic feature of extra-gonadal angiosarcomas (Fig. 1a). This is in contrast to a previous case of PPAS which demonstrated prominent internal vascularity on ultrasound [16]. Diagnosis is made following radical orchidectomy, by microscopic identification of characteristic morphologic features and confirmation employing immunohistochemistry. Nevertheless, this approach should be undertaken cautiously, since AS-GCT and PPAS are similar in both morphology and immunophenotype [4]. AS-GCT, however, demonstrates background germ cell tumour, whereas PPAS appears to arise de novo. Histologically, angiosarcoma comprises two main subtypes: classic (spindled cells) and epithelioid (plump epithelial-like cells). These malignancies also display variable architecture (solid or vasoformative) [4]. Epithelioid angiosarcomas are often macro- and microscopically similar to embryonal carcinomas [20, 22, 23]. They are distinguishable by subtle differences on microscopy and stain differently upon immunohistochemistry, however [20, 22, 23].

Initial misdiagnosis as embryonal carcinoma with teratoma occurred upon macroscopic and microscopic evaluation of two surgical AS-GCT specimens [22, 23]. Since embryonal carcinoma and epithelioid angiosarcoma often exhibit similar morphological characteristics, [22, 23] we highlight the importance of considering the diagnosis of angiosarcoma when examining unusual testicular malignancies, with use of appropriate immunohistochemistry if necessary. Accurate diagnosis of testicular angiosarcoma is of extreme clinical relevance. Missing this diagnosis indeed has a significant detrimental effect on patient management and prognosis [22, 23].

Local invasiveness was variable between cases of PPAS (Table 1). In the index case there was no evidence of local invasion, with two discrete lesions confined within the

Table 4 Disease progression, treatment and misdiagnosis of all known cases of AS-GCT

Case	Diagnosis				Treatment after angiosarcoma developed		Outcome at follow-up (time interval)
	Primary testicular diagnosis	Metastatic sites (tumour diagnosis)	Risk factors for angiosarcoma	Misdiagnosis	Chemotherapy	Surgery	
Primary angiosarcoma in germ cell tumour							
Malagón et al. [15]	Mature teratoma, yolk sac tumour, angiosarcoma	Retroperitoneum (N/A)	No	No	Cisplatin, Cyclophosphamide and Adriamycin	*N/A*	Alive with mets (8 months)
Malagón et al. [15]	Mature teratoma, angiosarcoma	Lungs, LNs (MT, AS)	No	No	Cisplatin, Cyclophosphamide and Adriamycin	*N/A*	Alive with mets (72 months)
Sahoo et al. [23]	Mature teratoma	Retroperitoneum (MT, AS), liver (AS), lungs, pleura (AS), retroperitoneal LNs (AS)	No	Yes, met: MT with epithelioid AS diagnosed as MT with embryonal carcinoma	Thalidomide Cisplatin and Gemcitabine	Resection, LND	Alive with mets (22 months)
Steele et al. [22]	Mature teratoma, epithelioid angiosarcoma	Lungs (AS), renal hilum (AS), pre-aortic, interaortocaval and renal hilar LNs (AS)	No	Yes, primary: MT with epithelioid AS diagnosed as MT with embryonal carcinoma	Cisplatin, Etoposide and Bleomycin Ifosfamide and Doxorubicin	Resection, RPLND	Alive with recurrent mets
Hughes et al. [20]	Mature teratoma, angiosarcoma	No	No	No	No	No	Alive with no mets (9 months)
Therapy-related angiosarcoma in germ cell tumour							
Idrees et al. [7]	Mature teratoma, seminoma, yolk sac tumour	Lungs (MT), retroperitoneum (MT), para-iliac, para-caval and retrocrural LNs (MT), LNs near thoracic duct (MT), posterior mediastinum (AS)	Cisplatin, Etoposide and Bleomycin (40 months) Vinblastine, Ifosfamide and Cisplatin (40 months)	No	No	6 Resections over 4 years	Alive with no mets (58 months)
Lee et al. [21]	Seminoma	Paravertebral (AS), lungs (AS), thorax (AS), liver (AS)	RT (10 years) Cisplatin, Vinblastine and Bleomycin (13 months)	No	MTX and leucovorin	Resections	Died (13 months after mets)
Ulbright et al. [6]	Mature teratoma	Retroperitoneum (MT), lungs, liver (AS), kidneys (AS), adrenals (AS), spleen (AS)	RT (5 years) Cisplatin, Vinblastine and Bleomycin (5 years)	No	No	No	Died (5 years)

rete testis and tunica albuginea. In the case of Piotrowski et al. [19] one tumour minimally extended into ipsilateral proximal spermatic cord and another into the epididymis. In the cases of Jain et al. [18] and Masera et al. [16] there was no local invasion. In the former case the entire testicular parenchyma was replaced by tumour and the patient complained of testicular firmness dating back ten years. In Armah et al. [17], there was invasion into the epididymis. We found no apparent explanation for the discrepancy in extent of local invasion between cases of PPAS.

The contralateral testis was not affected by metastatic disease in any of the cases of PPAS or AS-GCT. Metastatic sites of the PPAS and AS-GCT cases were similar to those of extra-gonadal angiosarcoma (Tables 2 and 4) [4].

Although extra-gonadal soft tissue angiosarcomas are associated with high rates of local recurrence [4], none of the thirteen testicular cases (index case included) experienced local recurrence following radical orchidectomy. This could be a consequence of negative surgical margins due to resection high up at the level of the spermatic cord, which enabled total oncological clearance via radical orchidectomy.

All cases of PPAS were treated using radical orchidectomy only (Table 2). In contrast, five of the eight cases of AS-GCT were treated using surgery with adjuvant chemotherapy after the angiosarcomatous component arose (Table 4). However, none of the chemotherapy regimens that were employed to treat AS-GCT eradicated disease [7, 13, 15, 21–23]. Surgery thus remains the most effective treatment for PPAS and AS-GCT. This is in keeping with extra-gonadal angiosarcomas, which also appear to be resistant to chemotherapies and radiotherapy [5, 15, 23]. Radical orchidectomy is also the mainstay surgical treatment for GCTs [8, 9, 26]. Platinum-based chemotherapy is the standard treatment for testicular germ cell tumours with heightened potential for metastasis or proven pre-existing metastasis [9, 27]. Teratomas are highly sensitive to cisplatin-based chemotherapy [9, 27]. Seminomatous metastases are particularly responsive to radiotherapy [28–30]. In general, testicular germ cell tumours are associated with excellent prognoses, even in the presence of metastatic disease [8–10].

Overall, two (40%) of the five PPAS cases suffered metastatic disease and died shortly thereafter, whereas three (60%) were alive without metastasis at follow-up, including the index case (Table 2). In contrast, only two (25%) of the eight cases of AS-GCT were alive without metastasis at follow-up and two (25%) had died (Table 4).

While follow-up was limited for most cases, survival for gonadal PPAS appeared superior to primary angiosarcoma that arises in extra-gonadal sites [1, 4, 15]. This is in keeping with a previous study that noted differential outcomes between testicular (gonadal) and mediastinal germ cell tumours (extra-gonadal) with sarcomatous transformation [15]. This might be because testicular angiosarcomas present earlier due to their location, ie easy access to self-examination, frequently prior to metastasis, and are amenable to complete resection using radical orchidectomy, compared to extra-gonadal angiosarcomas [4, 15].

In conclusion, PPAS is a rare testicular neoplasm. We present the fifth case in the literature. Clinical and radiological features are non-specific. The diagnosis is purely histological, with the pathologist choosing immunohistochemistry based on abnormal tumour morphology. Local invasiveness is variable but metastatic sites are typical for extra-gonadal angiosarcomas. PPAS confers a relatively better prognosis as compared to AS-GCT. While extra-gonadal angiosarcomas are associated with high rates of local recurrence following resection, in all cases of PPAS and AS-GCT there were no local recurrences following radical orchidectomy. Chemotherapy is associated with poor outcomes, thus surgical resection remains the most effective treatment for both subtypes of testicular angiosarcoma.

Abbreviations

AFP: Alpha-fetoprotein; AS: Angiosarcoma; AS-GCT: Angiosarcoma associated with germ cell tumour; CRP: C-reactive protein; CT: Chemotherapy; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; LNs: Lymph nodes; MDT: Multi-disciplinary team; Met: Metastasis; MT: Mature teratoma; MTX: Methotrexate; N/A: Not communicated in original case report; PPAS: Primary pure angiosarcoma; RPLND: Retroperitoneal lymph node dissection; RT: Radiotherapy; β-HCG: Beta-human chorionic gonadotrophin.

Acknowledgements

The authors thank James Arrich for his contribution to the tabulated summaries, and Brendan Berry for the acquisition of the ultrasound images.

Authors' contributions

JWE wrote the first draft of the paper and edited at later stages. MY coordinated all author efforts, wrote and edited the paper and managed patient communication. JWE and MY contributed equally to the paper. SG wrote and edited the paper and assembled all graphics. DA generated and analysed histopathological data, wrote and edited the paper. SC made first contact with the patient, held final responsibility pertaining all clinical activities concerned, conceived the study and edited the paper. All authors read and approved the final manuscript.

Funding

No funding applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request, pending patient consent.

Ethics approval and consent to participate

Ethics approval was waived.

Consent for publication

Written and signed consent to publish the case was obtained from the patient.

Competing interests
The authors declare that they have no competing interests.

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Received: 19 May 2020 Accepted: 21 October 2020
Published online: 31 October 2020

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