CORRESPONDENCE

Signet ring stromal tumours of testis: a tale of two cases on a morphological spectrum

To the Editor,
Signet ring stromal tumour of testis (SRSTT) is an extremely rare tumour, which has only been recently described and has also been included in the World Health Organization (WHO) classification of urinary and male genital tumours (5th edition).1,2 Another similar testicular entity, with limited published data, is pancreatic analogue solid pseudopapillary neoplasm of the testis (PA-SPN). These tumours have been described in the ovary but the data in testis is limited.3 SRSTT and PA-SPN share a degree of morphological overlap and have immunohistochemical and molecular similarity to each other, and also with the pancreatic solid pseudopapillary neoplasm.4 We report two cases (one each of SRSTT and PA-SPN) of this entity, lying on different aspects of its morphological spectrum.

Case 1 was a 79-year-old man who presented with enlarged right testis. Ultrasound examination revealed a heterogeneous hypoechoic round lesion measuring 50 × 43 × 41 mm. Serum tumour markers were within normal limits. Computed tomography (CT) showed no evidence of metastatic disease. The patient underwent right inguinal orchidectomy. Macroscopic examination revealed a well circumscribed 49 mm tumour replacing the entire testicular parenchyma. Microscopy showed a tumour composed of cells with cytoplasmic vacuolation with signet-ring appearance (Fig. 1). The cells were separated by fibrovascular septa, giving a lobulated appearance. There were no sarcomatous areas identified. Immunohistochemistry showed the tumour cells to be positive for CD10, vimentin, NSE, S100 (focal) and β-catenin (nuclear). They were negative for cytokeratins (AE1/AE3, CAM5.2), inhibin, calretinin, Melan-A, HMB-45, chromogranin, synaptophysin, CD68, PAX8, NKKX3.1, Glypican 3, CD117, D2-40, SALL-4, OCT3/4 and PLAP. There was no amplification of MDM2 or rearrangement of EWSR1 or FUS (tested by fluorescence in situ hybridisation). Next generation sequencing (NGS)-based molecular testing was performed which revealed that the tumour harboured the CTNNB1 p.(Asp32Tyr) (exon 3) mutation. The final diagnosis of primary SRSTT was made. With a lack of evidence of benefit for adjuvant treatment of these tumours and the indolent natural history reported in the literature available, no adjuvant treatment was offered. The patient continues active surveillance per local guidelines for non-seminomatous germ cell tumour. There are no signs of recurrence now 18 months post-hemiscrotectomy.

Case 2 was a 47-year-old male patient referred by his general practitioner with a mass in his upper right scrotum. Ultrasound showed an irregular hypoechoic ovoid lesion, 0.5 cm below the skin surface. There was no other FDG avid lesion. A wide local excision of the upper right scrotum was performed. The macroscopic examination of the hemiscrotectomy showed a well circumscribed, rounded 30 mm tumour. On microscopic examination the tumour was highly cellular and had a nodular growth pattern. The nodules had a solid and papillary architecture, with papillae lined by relatively uniform, small, cuboidal cells with round nuclei and moderate amounts of pale staining finely granular eosinophilic cytoplasm (Fig. 2). The tumour nodules were separated by fibrous septa. Immunostaining demonstrated diffuse positive staining for CD56, synaptophysin, glypican 3, β-catenin (nuclear), CD10, NSE and vimentin. Immunostaining for AE1/AE3, LMCK, E-cadherin, HMCK, inhibin, calretinin, WT-1, SF-1, SALL4, PLAP, Oct3/4, AFP and chromogranin was negative. NGS-based molecular testing was performed which revealed that the tumour harboured the CTNNB1 p.(Asp32Tyr) (exon 3) mutation. The morphology and immunoprofile was suggestive of a PA-SPN of testis. The patient had a history of radical inguinal orchietomy in 2012 which, at that time, was reported as a neuroendocrine tumour. Those slides were reviewed and were found to have similar histology to the current presentation and the diagnosis was amended to PA-SPN of testis. Like Case 1, with no evidence for adjuvant treatment benefit, the patient continues active surveillance per local guidelines for non-seminomatous germ cell tumour. There are no signs of recurrent disease now 2 years post-hemiscrotectomy.

Both SRSTT and PA-SPN are relatively recently described entities with only limited published literature.1–4 A review of the literature revealed that only 22 such cases have been described in the literature so far.1–6 The age range of patients with these tumours varies from 23 to 82 years, with a mean age of 43 years. The size of the reported tumours has varied from 5 to 48 mm.

Pancreatic solid pseudopapillary neoplasm (PSPN) is a well documented entity, commonly identified in the tail of the pancreas.7 This tumour is commonly seen in young females, where it presents as a large mass. Histologically, it is composed of poorly cohesive cells arranged in the form of solid sheets and with a pseudopapillary pattern. It is also common for these tumours to show areas of hyalinisation, haemorrhage, calcification and cholesterol cleft formation. The neoplastic cells have uniform nuclei with fine chromatin, inconspicuous nucleoli and characteristic longitudinal grooves. This makes pancreatic neuroendocrine tumour a common differential diagnosis of PSPN. However, this differentiation can easily be made with the help of immunohistochemical markers, where PSPN shows expression of nuclear β-catenin, CD10, galectin-3 and cyclin D1. They usually lack the expression of chromogranin, however a proportion of cases do show the expression of synaptophysin, CD56 and NSE.8 Both tumours that we present (one each of PA-SPN and SRSTT) show similar phenotypic profile with the expression of nuclear β-catenin, CD10 and NSE. The PSPN can also arise at extra pancreatic sites, especially in the setting of pancreatic heterotopia. However, occurrence of this entity in other organs is extremely rare. The most common extra pancreatic site reported is ovarian.9 There are only seven cases of PA-SPN described in the testicular location.1,5,6 These tumours predominantly showed solid pseudopapillary architecture and were devoid of signet ring cells. In contrast,
of the eight cases SPN of the pancreas studied by Michalova et al. there was some component of signet ring cells in six of the tumours.6

Michalova et al. described 13 cases of SRSTT, of which seven had an exclusively signet ring cell component, while six had some component with morphology of SPN.4 The immunohistochemical profile of both the components was also found to be similar with the expression of nuclear β-catenin, cyclin D1, CD10, NSE, CD56, α-1-antitrypsin, vimentin, galectin-3, and claudin 7, with lack of expression for chromogranin, sex cord markers, and germ cell markers. This similarity in the immunohistochemical profile and the presence of both the components in the same tumour, clearly indicates that these two tumours (SRSTT and PA-SPN) represent similar (if not the same) neoplastic process. The immunoprofile of PA-SPN was found to be similar to that of pancreatic SPN.6

PSPN has been known to harbour mutations in the exon 3 of β-catenin gene (CTNNB1). This mutation has also been described in the ovarian cases of extra pancreatic SPN.9 The only reported case of PA-SPN also had this mutation.1 Similarly, all 13 cases of PSRSTT had this mutation. The six cases of PA-SPN described by Michalova et al., showed a similar mutational profile, as identified in the SPN of the pancreas.6 β-catenin is an intermediary in the Wnt/β-catenin pathway. In the event of its mutation, there is abnormal stabilisation and nuclear accumulation of β-catenin. In the nucleus β-catenin associates with Tcf/Lef and leads to increased cell proliferation.5,10 We performed a 70-gene panel and demonstrated CTNNB1 exon 3 mutations in both the tumours.

In the largest published series, the authors hypothesised that the signet ring cell component is present in the initial stages and as the tumour enlarges, the solid pseudopapillary

Fig. 1  Case 1: (A) H&E low power, (B) H&E high power, (C) CD10, (D) vimentin, (E) NSE, (F) S100.

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component becomes more dominant. They also found that the exclusive SRSTT were smaller tumours and the SPN component became more obvious with the increasing size. Both reported tumours in this current report were comprised of only one of either solid pseudopapillary or signet ring cell. Interestingly, the SRSTT (Case 1) was a larger tumour (49 mm) in comparison to PA-SPN (Case 2), which was smaller (30 mm). This goes against the hypothesis postulated by Michalova et al.

Assessment of prognosis is difficult, limited by the small number of cases reported, but most of the reported cases appear to be indolent in nature. It remains to be seen whether poor prognostic factors seen in pancreatic SPNs, such as size larger than 5 cm, occurrence in males, the presence of necrosis and cellular atypia, vascular invasion, or invasion into adjacent structures, are applicable to testicular tumours. However, it is worth noting that in the pancreas, surgical resection is curative in more than 95% of cases. In our case of PA-SPN, the tumour had recurred locally within the scrotum, and focal necrosis was also present, suggestive of a more aggressive behaviour. This is, to our knowledge, the first reported case of PA-SPN with recurrence.

In response to the case series by Michalova et al., Ulbright and Young postulated that SPPN-like tumours in the testis may represent a variant of a Sertoli cell tumour and may be more appropriately designated Sertoli cell tumour, not otherwise specified. However, our case lacked expression of sex cord stromal markers and areas showing classic tubular morphology.

In conclusion, we present two cases of rare but likely related entities of primary testicular signet ring stromal tumour and pancreatic analogue solid pseudo-papillary
neoplasm, which expand the reported clinical and morphological spectrum of these newly reported entities. These tumours share morphological and molecular similarities and appear to demonstrate indolent biological behaviour. However, in presenting the first case of a recurrent testicular SPN, we demonstrate the need for further categorisation of these lesions.

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