

Oncology

Epstein Barr virus-associated smooth muscle tumour (EBV-SMT) of the urinary bladder

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1. Introduction

Epstein-Barr virus-associated smooth muscle tumour (EBV-SMT) is an uncommon, under-recognised but distinct clinicopathological entity that occurs in the setting of immunosuppression. Predisposition of organ transplant patients to smooth muscle tumours was originally recognised by Pritzker et al., in 1970¹ and the link to EBV infection was first reported by a French pathologist in 1994.² The following year, two groups of US researchers separately reported on handful of paediatric patients with EBV associated smooth muscle tumours in the setting of organ transplant³ and HIV,⁴ respectively. To date, over 200 cases have been reported in the English literature. It is seen in post organ or stem cell transplant patients, HIV/AIDS and congenital immunodeficiencies.

1.1. Case presentation

A 35 year old woman from Papua New Guinea was referred to our tertiary centre with obstructive urinary tract symptoms. Her symptoms developed during pregnancy over 6 months and required an indwelling catheter for acute urinary retention. Her medical history is significant for positive HIV serology and she is currently on antiretroviral therapy - Lopinavir/Ritonavir (200/50 mg) twice daily and Lumivudine/Tenofovir (300/300 mg) nightly. CD4 count at presentation was 0.43×10^9 and her HIV viral

load was 398 RNA/ml. Radiological examination of the pelvis showed a 7.0×5.0 cm mass involving the bladder neck and vaginal wall (Fig. 1A–C). Three neoplastic lesions measuring up to 7.9 cm were also identified in the liver on further imaging, raising possibility of a pelvic malignancy with hepatic metastases. Cystoscopy and biopsy were performed and a mobile soft 15 cm mass attached to the right urethral wall, bladder, and vaginal walls was biopsied.

On histopathological examination the tumour comprised short fascicles of spindle cells with blunt ended nuclei and moderate amounts of eosinophilic cytoplasm. There were scattered aggregates of lymphoplasmacytic cells together with thin walled, ectatic staghorn-type vessels (Fig. 2A–C).

Immunohistochemistry showed strong and diffuse staining for smooth muscle actin (SMA) and h-caldesmon. CD3 highlighted T cells in the background. Desmin, ALK-1, CD34, DOG1, CD117, CD99, GATA3 and keratins were negative. EBER-ISH was positive in most neoplastic cells. (Fig. 3A–C). A histopathological diagnosis of Epstein-Barr virus-associated smooth muscle tumour (EBV-SMT) of the urinary bladder was rendered.

2. Discussion

The tumour has a predilection for sites 'unusual' for typical leiomyoma and leiomyosarcoma such as liver, lung, brain and head & neck region. Only a handful of EBV-SMTs have been described in the genitourinary tract (adrenal glands, kidney and bladder). Multiple lesions in more than one organ are seen in 68% of cases and gene profiling studies looking at clonality of EBV in individual cases have shown that concurrent tumours arise from recurrent infections with the virus rather than from metastases.

Microscopically, the tumour shows intersecting fascicles of spindle cells with smooth muscle morphology and scattered CD3 positive T-lymphocytes in the background. The tumour also differs from usual smooth muscle tumours in having occasional aggregates of so-called primitive round cells. On immunohistochemistry, SMA is invariably positive but only half of the cases are desmin positive. EBER-ISH is positive in all tumours described to date and is sine qua non for a correct histopathological diagnosis. Mitotic activity, presence of necrosis and cytological atypia are variable and of no

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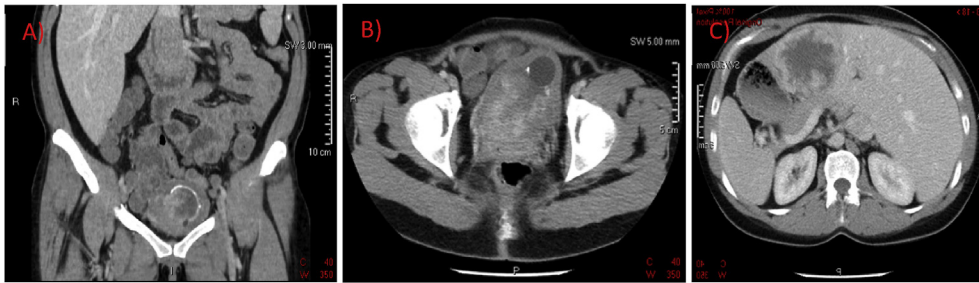


Fig. 1. A) Coronal and B) Axial CT sections of large bladder tumour C) Axial CT Section of hepatic mass.

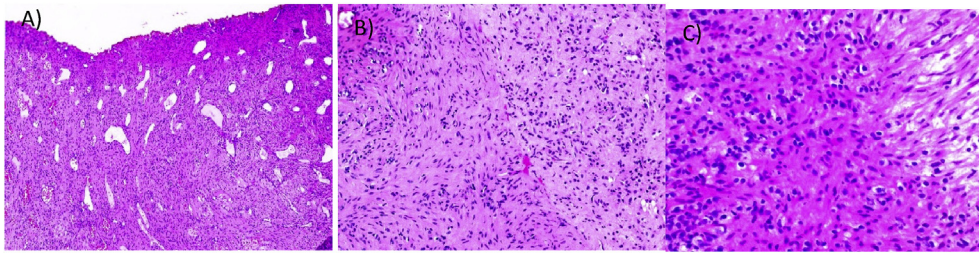


Fig. 2. A) Low power view showing a cellular spindle cell lesion with short staghorn-type vessels in the background. B) Medium power view showing short fascicles and scattered lymphoplasmacytic cells. C) So-called 'primitive round cells' characteristic of this lesion were evident in a subsequent transurethral bladder resection.

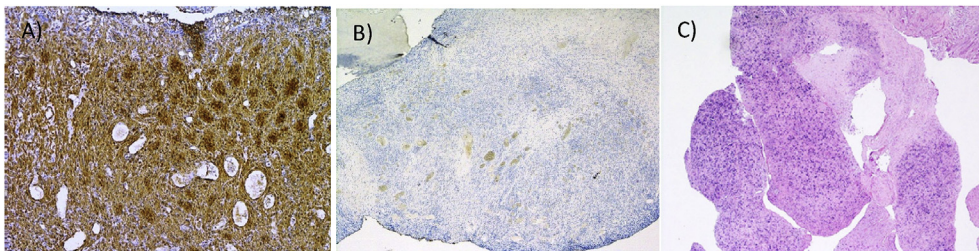


Fig. 3. A) Neoplastic cells show diffuse and strong positive staining for SMA. H-caldesmon was similarly positive. B) Desmin is negative. C) EBER-ISH is diffusely positive.

clinical or prognostic significance in this lesion.

The differential diagnosis of EBV-SMT in the urinary bladder includes other intramural spindle cell neoplasms such as leiomyoma, inflammatory myofibroblastic tumour, post-operative spindle cell nodule, extra-gastrointestinal gastrointestinal stromal tumour (GIST), leiomyosarcoma and rhabdomyosarcoma.

Due to its rarity and unpredictable behaviour, optimal management for EBV-SMT is unknown. However, the tumour appears to respond to reduced immunosuppression, surgical resection and chemotherapy in reported cases. Small case series have found no significant differences in overall survival between surgical resection and reduced immunosuppression without surgery, indicating that both strategies may be used.⁵ Optimising anti-retroviral treatment is also recommended for AIDS related cases. Recent studies have suggested an association between EBV-SMT and the activation of the AKT/mammalian target of rapamycin (mTOR) signal pathway and treatment with Sirolimus, an AKT/mTOR signal inhibitor is currently under investigation.

Prognosis of EBV-SMT appears to correlate more with the status of patients' immunity status than with conventional histopathological features of malignancy (size, mitotic activity, necrosis, cytological atypia and margin status). HIV associated EBV-SMT patients have a worse prognosis than post-transplant related and congenital immunodeficiency cases. Multi-organ disease and

intracranial involvement also confers a worse prognosis than uni-organ and extracranial disease, respectively.⁵

Overall, clinical outcome for this neoplasm is worse than that of usual-type leiomyoma and better than that of leiomyosarcoma, with most patients dying of immunosuppression related causes such as opportunistic infections and acute rejection rather than from tumour progression. In largest studies available to date, mortality is in the order of 30% with a median survival of 5.5 months.⁵

Following resection of the bladder lesion, she underwent a successful trial of void and had return of normal voiding function. The liver lesions were managed conservatively by the hepatobiliary team, with a plan to surveil with liver ultrasound in 3 months. Her anti-retroviral therapy was also optimised. She then returned to Papua New Guinea and declined further clinical follow-up at our centre, including telehealth appointments.

3. Conclusions

In summary, EBV-SMT is a distinct clinicopathological entity that should be distinguished from mimickers such as usual-type leiomyoma and leiomyosarcoma. Histopathological criteria for smooth muscle malignancy do not apply to this lesion. Presence of concurrent lesions in other organs such as liver and lung is not

evidence of metastasis.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eucr.2017.11.015>.

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