

Case report

Plasmacytoid urothelial carcinoma; A series of two cases and the approach to diagnosisL.J. De Silva¹, W.S.L. De Silva², H.D. Wijesinghe¹, W.A.S. de Silva², A.P. Malalasekara³, M.V.C. de Silva¹¹Department of Pathology, Faculty of Medicine, University of Colombo, Sri Lanka.²Institute of Urology, National Hospital of Sri Lanka, Colombo, Sri Lanka.³Department of Anatomy, Faculty of Medicine, University of Colombo, Sri Lanka.

Submitted on 23.04.2021 Accepted for publication on 24.09.2021

Abstract

Plasmacytoid urothelial carcinoma (PUC) is a rare and aggressive variant of urothelial carcinoma. PUC can occur in any part of the urinary tract, but the upper ureteric origin is extremely rare, with only two cases reported to date. The diagnosis of this specific variant of urothelial carcinoma has prognostic implications and necessitates close oncological follow up after surgical resection.

We report two cases of urothelial carcinoma with plasmacytoid differentiation in two different locations of the urinary tract. The first case was of a 59-year-old man who was investigated for right loin pain. He was found to have a lesion in the right upper ureter with imaging evidence of right side hydronephrosis and upper hydroureter. The lesion was sampled with ureteroscopic washings and cup biopsy and later underwent a right nephroureterectomy following the diagnosis of urothelial carcinoma. The second case was of a 77-year-old man who was investigated for painless macroscopic haematuria. Imaging revealed a lesion in the anterior wall of the

bladder. Transurethral resection of bladder tumour was performed.

Histology and immunocytochemistry of both lesions were compatible with PUC.

These cases highlight the importance of identifying and reporting this rare variant of invasive urothelial carcinoma as it has a poor outcome compared to usual urothelial carcinoma.

Keywords: plasmacytoid urothelial carcinoma, urothelial carcinoma, plasmacytoma

Introduction

Urothelial carcinoma accounts for more than 90% of all bladder carcinomas and exhibits divergent morphological patterns in pure or combined forms (1). According to the 2016 World Health Organization classification of tumours, thirteen different histological variants of infiltrating urothelial carcinoma are recognized (2,3). PUC is a rare, aggressive variant with an incidence of 1-3 % of invasive urothelial carcinomas (1). Most PUCs have been reported in the bladder. Primary PUC in the upper ureter is extremely rare, with only two reported cases in the English literature (4, 5). The histological diagnosis of PUC is

Corresponding author: Dr Lalani De Silva
Lecturer and Senior Registrar
Department of Pathology, Faculty of Medicine
University of Colombo, Sri Lanka
lalanidesilva7@gmail.com



This is an open access article licensed under a [Creative Commons Attribution-ShareAlike 4.0 International License](https://creativecommons.org/licenses/by-sa/4.0/). (CC BY-SA 4.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are attributed and materials are shared under the same license.

challenging when it occurs in pure morphological patterns. Here we report two cases of pure PUC occurring in two different locations of the urinary tract, one of which is the third reported case of PUC originating in the upper ureter. The histological differential diagnoses are discussed.

Case report

Case 01: A 51-year-old man presented with vague right loin pain for one year. He denied haematuria and had no constitutional symptoms. He was a heavy smoker and had smoked 20 pack years. As per his comorbidity profile, he had diabetes mellitus, hypertension and hyperlipidaemia, and had undergone coronary artery bypass grafting five years ago. Basic investigations, including leukocyte count, liver and renal function tests were within normal limits. The ultrasound scan of the kidney ureter bladder (USS-KUB) revealed moderate hydronephrosis and an upper hydroureter on the right side. However, the cause was not apparent. A 1.0×1.5 cm enhancing lesion was identified in the upper ureter 2 cm distal to the pelviureteric junction, in the computerized tomography (CT),

accompanied by right hydronephrosis and upper hydroureter (Figure 1).

Upon ureteroscopic examination, a flattened lesion of 1.0×1.5 cm was identified in the upper ureter, completely blocking the lumen. Therefore, the ureter proximal to the lesion was not intubated. Ureteroscopic washings for cytology and a cup biopsy for histology were obtained, and a diagnosis of PUC was made on both cytological and histological examinations. The patient underwent a right nephroureterectomy. The tumour was in the upper ureter and renal pelvis. Histological examination of the resected specimen confirmed the presence of a pure PUC with no conventional urothelial carcinoma or non-invasive component (Figure 2). The tumour invaded the muscle wall but was confined to the ureter (stage pT2), and the ureteric margin was free from tumour. The immediate post-operative period was uneventful. He was followed up in both urological and oncological clinics, and the initial follow up cystoscopy and biopsy were normal. However, owing to the aggressive nature of this variant, the patient presented with multiple recurrences in the bladder, ultimately requiring



Figure 1: CT images of Case 01. **a.** Axial image of the enhancing tumour (star) in the upper ureter 1.5 cm distal to PUJ with resultant hydronephrosis and hydroureter on the right side. **b** CT-IVU demonstrating no excretion of the contrast on the right side (arrow) due to the complete occlusion of the ureter by the tumour.

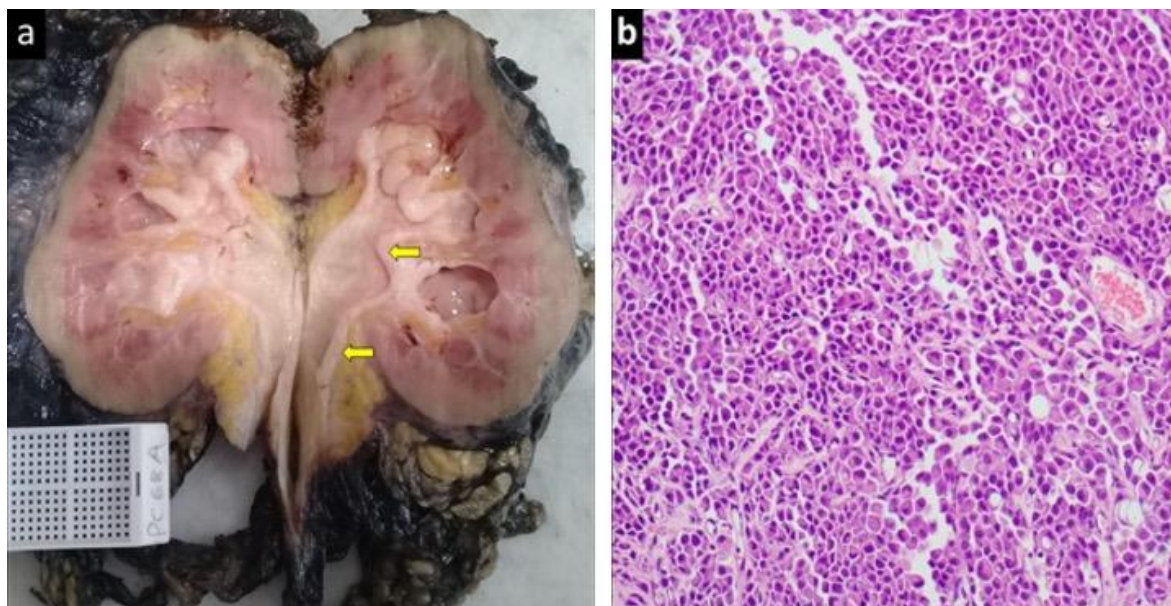


Figure 2: Case 01. a. Gross appearance of the resected specimen - the tumour in the upper ureter and irregular thickened wall of the renal pelvis (arrows). b. Microscopy of the tumour showing sheets of atypical plasmacytoid cells (H&E x200).

cystoprostatectomy within six months of the initial diagnosis.

Case 02: A 77-year-old man presented with painless macroscopic haematuria of two months duration. He was a non-smoker and had no other comorbidities. Physical examination was unremarkable. Basic haematological and serological investigations were within normal limits. USS revealed a 2.0x2.0 cm nodular mass attached to the anterior bladder wall. The ureters were normal. CT scan confirmed the presence of a non-muscle invasive bladder tumour. Transurethral resection was performed, and the microscopy of resected bladder chippings confirmed the presence of a PUC (Figure 3). It was a non-muscle-invasive carcinoma and staged as pT1. Eight weeks later, the scar in the bladder was re-resected, and there was no evidence of recurrent or residual tumour. At present, he is awaiting review by the oncologist.

Histological examination of both tumours showed cellular tumours with minimal stroma.

There were sheets of discohesive, large, atypical plasmacytoid cells with frequent mitoses. There were areas of spotty necrosis. Despite extensive sampling, no conventional urothelial carcinoma component was found. On immunohistochemical analysis the plasmacytoid cells of both tumours stained diffusely with CD138, CK7 and CK20 and were negative for E-cadherin, LCA, CD20, MUM1 and CD56, compatible with PUC.

Discussion

PUC was first reported three decades ago as a metastatic bone deposit of urothelial carcinoma (6). The presence of solid sheets, nests or an alveolar pattern comprising monotonous, large, discohesive cells with plasmacytoid morphology, characterized by eccentrically located rounded nuclei and abundant amphophilic to eosinophilic cytoplasm is diagnostic of this variant. Some cells may exhibit perinuclear haloes similar to plasma cells. In addition, tumours with signet ring cells unassociated with extracellular mucin are also incorporated into this category (2, 3).

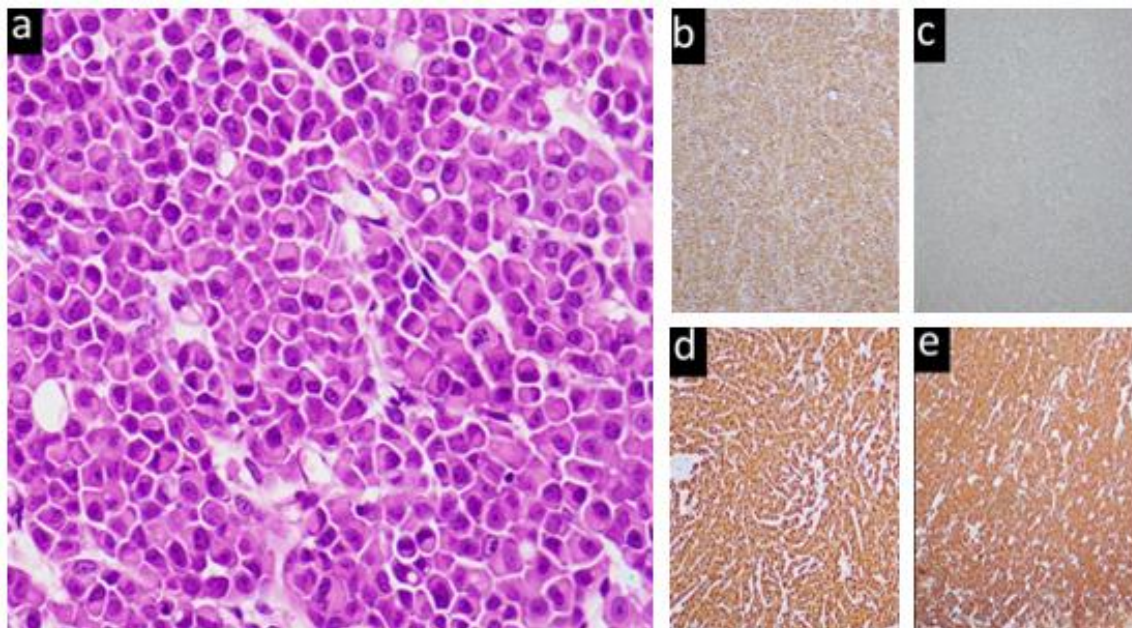


Figure 3. Case 02 a. Microscopy of the tumour showing mitotically active pleomorphic plasmacytoid cells (H&E x400) b. CD138 - Diffusely positive (IHC x100), c. E-cadherin - Negative (IHC x100) d. CK7- Positive (IHC x100).

It is an aggressive variant with frequent muscle invasion, extravascular extension, relapses and metastases. Therefore, the overall prognosis is poor (2, 3, 7).

Approximately half of the reported PUC are associated with conventional urothelial carcinoma which helps to confirm its urothelial origin (2,3). The absence of conventional urothelial carcinoma, results in a pure PUC, as in these two cases which is diagnostically challenging. The differential diagnoses include plasmacytoma, secondary deposits of invasive lobular breast carcinoma or deposits of a poorly cohesive carcinoma of the stomach. Rare possibilities include rhabdomyosarcoma, urothelial carcinoma with rhabdoid features, deposits of melanoma or large cell lymphoma (7). In this setting, clinical history may provide important clues to the diagnosis, but history alone is inadequate to arrive at a definitive diagnosis. Similarly, radiology plays a limited role (7).

Immunohistochemistry is an invaluable adjunct in tissue diagnosis, as it is impossible to differentiate pure PUC from its mimickers on

features of the routinely stained sections alone. PUC is positive for both high molecular weight cytokeratin (HMWCK) and low molecular weight cytokeratin (LMWCK), CK7, CK20 and 34 β E12. However, cytokeratin positivity may be observed in plasmacytoma. Positivity for both HMWCK and LMWCK is unlikely in lobular breast carcinoma and poorly cohesive gastric carcinoma. CD138, the recognized plasma cell marker, is known to exhibit positivity in one-third of PUC. Kappa and lambda light chain restriction had been detected in a minority of PUC (1, 3, 7). This is a potential pitfall for distinguishing plasmacytoma from PUC. Both our cases showed positivity for LMWCK (CK7 and CK20) and CD138. Uroplakin II, uroplakin III and GATA 3 are considered as specific markers of urothelial carcinoma and are positive in 33%, 8% and 80% of PUC, respectively. Uroplakin II is a more sensitive and specific marker than uroplakin III (1, 3, 7).

GATA 3 has limited value in differentiating PUC from metastatic deposits of lobular breast carcinoma as it is expressed in both tumours. Similarly, a considerable proportion of PUC are

positive for progesterone receptors (PR) and Her-2. However, it has been shown that PUC does not express oestrogen receptors (ER) and mammaglobin. ER and mammaglobin positivity can reliably be used to differentiate lobular breast carcinoma deposits from PUC although 30% of lobular breast carcinomas are mammaglobin negative. The value of GCDFP-15 is limited in this setting as about 24 % of PUC are known to express positivity (8).

Differentiation of PUC from metastatic deposits of poorly cohesive carcinoma of the upper gastrointestinal tract is challenging since both CDX2 and CEA are positive in PUC. But uroplakin II and GATA 3 can be used to identify the urothelial origin in this setting (1, 7, 8).

The possibility of a plasmacytoma was excluded by the negativity of LCA, CD20, MUM1 and CD56 in these two tumours. Due to the unavailability of specific urothelial markers in our setting, the possibility of metastatic deposits of lobular breast carcinoma and poorly cohesive adenocarcinoma were excluded by detailed clinical assessment and radiological survey.

Loss of E-cadherin adhesion molecule is mostly a result of a mutation in the CDH-1 gene. The cellular discohesion is explained by loss of E-cadherin in approximately 76.2% of PUC, while the negativity is seen only in 11.1% of conventional urothelial carcinoma. However, as E-cadherin negativity is seen in all its mimickers, including plasmacytoma, this has limited value in the diagnostic process of PUC (9).

The retinoblastoma (RB) gene mutation is detected in 62% of patients with PUC (9). Even though the aggressive nature of this variant is associated with RB gene mutation, its presence makes it a suitable candidate for RB targeted therapy. Some PUC express PD-L1 which helps to evade the immune system, and if expressed, it makes the tumour eligible for PD-L1 targeted therapy (1, 7, 9, 10).

Management of PUC is debatable. Radical cystectomy and chemotherapy are considered as general modes of management. Considering the poor overall outcome of PUC, an aggressive treatment protocol is recommended from the beginning irrespective of the tumour stage. (10).

Conclusion

Although the diagnosis of pure PUC is challenging and requires extensive clinical, radiological and histopathological evaluation, a correct and timely diagnosis is extremely important in the management of this aggressive variant of urothelial carcinoma.

References

1. Fox MD, Xiao L, Zhang M, Kamat AM, Siefker-Radtke A, Zhang L et al. Plasmacytoid urothelial carcinoma of the urinary bladder: a clinicopathologic and immunohistochemical analysis of 49 cases. *American Journal of Clinical Pathology*. 2017;147(5):500-6.
<https://doi.org/10.1093/ajcp/aqx029>
2. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—Part B: Prostate and bladder tumours. *European Urology*. 2016;70(1):106-19.
<https://doi.org/10.1016/j.eururo.2016.02.028>
3. Moch H, Humphrey PA, Ulbright TM.(Eds) WHO classification of tumours of the urinary system and male genital organs. Lyon: IARC Press; 2016.
4. Chang IW, Hsu CT, Huang CY, Tsai JW. Plasmacytoid urothelial carcinoma: First case reported in the ureter. *Pathology International*. 2013;63(1):73-6.
<https://doi.org/10.1111/pin.12026>
5. Jibril A, Stevens AC. Plasmacytoid urothelial carcinoma of ureter with retroperitoneal metastasis: A case report.

- American Journal of Case Reports. 2018;19:158-162.
<https://dx.doi.org/10.12659%2FAJCR.906679>
6. Sahin AA, Myhre M, Ro JY, Sneige N, Dekmezian RH, Ayala AG. Plasmacytoid transitional cell carcinoma. Report of a case with initial presentation mimicking multiple myeloma. *Acta Cytologica*. 1991;35(3):277-80.
 7. Sood S, Paner GP. Plasmacytoid urothelial carcinoma: an unusual variant that warrants aggressive management and critical distinction on transurethral resections. *Archives of Pathology & Laboratory Medicine*. 2019;143(12):1562-7. <https://doi.org/10.5858/arpa.2018-0139-RS>
 8. Keck B, Stoehr R, Wach S, Rogler A, Hofstaedter F, Lehmann J. et al. The plasmacytoid carcinoma of the bladder—rare variant of aggressive urothelial carcinoma. *International Journal of Cancer*. 2011;129(2):346-54.
<https://doi.org/10.1002/ijc.25700>
 9. Guo CC, Czerniak B. Bladder cancer in the genomic era. *Archives of Pathology & Laboratory Medicine*. 2019;143(6):695-704. <https://doi.org/10.5858/arpa.2018-0329-RA>
 10. Horwich A, Babjuk M, Bellmunt J, Bruins HM, De Reijke TM, De Santis M. et al. EAU–ESMO consensus statements on the management of advanced and variant bladder cancer—an international collaborative multi-stakeholder effort: under the auspices of the EAU and ESMO Guidelines Committees. *Annals of Oncology*. 2019;30(11):1697-727.
<https://doi.org/10.1093/annonc/mdz296>