Quiz Case

A small round blue cell tumor in urine: cytomorphology and differential diagnosis

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CLINICAL HISTORY

This was a male patient in his late 70s presented with hematuria. He had Merkel cell carcinoma (MCC) of the right flank skin 5 years ago; diffuse large B-cell lymphoma (DLBCL) involving lymph nodes in the neck, retroperitoneum, and groin 2 years ago; and conventional prostatic adenocarcinoma 1 year ago. Cystoscopy showed a mass at the right side of the bladder wall. Bladder washing and biopsy were performed. The urine cytology and cell block sections showed scattered atypical cells [Figure 1]. The atypical cells were positive for CK20, MCPyV, and SATB2 immunostains and negative for CD20, PSA, P63, and GATA3.

QUESTION

Q1. What is your interpretation?
   a. Diffuse large B-cell lymphoma
   b. Metastatic prostatic adenocarcinoma
   c. Squamous cell carcinoma
   d. High-grade urothelial carcinoma
   e. Metastatic Merkel Cell Carcinoma (MCC).
ANSWER

The correct interpretation is E: Metastatic MCC.

EXPLANATION

Cytopathologic examination of the urine revealed scattered discohesive atypical cells of a small round blue cell tumor, in a background of abundant neutrophils and reactive urothelial cells [Figure 2]. The tumor cells were small to medium sized (about 2–4 times of a lymphocyte), with high N/C ratios and scant basophilic cytoplasm. The nuclei were round, centrally located, with mild nuclear irregularities, stippled chromatin and inconspicuous nucleoli.

Due to the clinical history of multiple malignancies, immunohistochemical studies were performed on both the cell block and the bladder biopsy. Tumor cells are negative for CD20, which makes DLBCL unlikely. Tumor cells are negative for PSA, which does not support metastatic prostatic adenocarcinoma. Tumor cells are also negative for P63 and GATA3, excluding primary bladder squamous cell carcinoma and high-grade urothelial carcinoma, respectively. The atypical cells were positive for CK20, MCPyv, and SATB2 [Figure 3] and focally weakly positive for Synaptophysin, which support the diagnosis of metastatic MCC.

ADDITIONAL QUIZ QUESTIONS

Q2. Which virus is associated with MCC?
   a. BK virus
   b. JC virus
   c. MCPyv
   d. SV40
   e. HPV

Q3. Which of the following immunostain results are most likely seen in a metastatic MCC?
   a. Synaptophysin+, Chromogranin+, TTF-1-, SATB2+, CK20+
   b. Synaptophysin+, Chromogranin+, TTF-1+, SATB2-, CK20-
   c. Synaptophysin-, Chromogranin-, GATA3+, SATB2-, CK20+
   d. Synaptophysin-, Chromogranin-, TTF-1-, SATB2-, CD20+
   e. Synaptophysin+, Chromogranin+, FLI-1+, SATB2-, CK20-

Q4. When a malignant small round blue cell tumor is seen in urine cytology, the differential diagnosis should include:
   a. Small cell carcinoma
   b. Metastatic MCC
   c. Lymphoma
   d. High-grade urothelial carcinoma
   e. All of above.

Answers to additional quiz questions
   a. Q2: C
   b. Q3: A
   c. Q4: E.

EXPLANATION

Q2: More than 80% of the MCCs are associated with MCPyv infection. MCPyv is a non-enveloped double-stranded DNA virus. Although it belongs to polyomavirus family, it is distantly related to SV40 virus and has less cross-reaction with SV40 antibody (clone PAb416) than BK and JC viruses. A more specific antibody (clone CM2B4) has better detection rate of MCPyv.[1] Our case showed MCPyv CM2B4 clone positivity and SV40 antibody negativity, supporting the published results. Therefore, the use of SV40 immunostain in MCC is not recommended.

Q3: Metastatic MCC in urine shows typical neuroendocrine tumor cytomorphology, such as high N/C ratios and stippled chromatin. Immunohistochemical studies can aid the diagnosis. Most MCCs are positive for CK20 with membranous and/or perinuclear dot-like staining pattern. MCC is usually positive for one or multiple neuroendocrine markers, such as synaptophysin, chromogranin, CD56, and neuron-specific enolase. SATB2 is a nuclear matrix-associated protein expressing in Merkel cells and has been recently recognized as a highly specific marker for MCC[2] and is positive in our case.

Q4: In urine cytology, when atypical small round blue cells are seen, the differential diagnosis includes but not limited to small cell carcinoma (SmCC), lymphoma, and high-grade urothelial carcinoma.

Primary SmCC of the urinary bladder is rare and is morphologically indistinguishable from metastatic SmCC or metastatic MCC. In addition, primary SmCC, metastatic SmCC, and metastatic MCC all express neuroendocrine markers, which make differentiation extremely difficult.
Coexistence of urothelial carcinoma will favor primary SmCC in the urinary bladder. TTF-1 immunostain positivity favors SmCC over metastatic MCC. On the other hand, SATB2 positivity will support metastatic MCC. Of course, correlation with clinical history and imaging studies is very important.

Lymphoma in urine shows single atypical cells with high N/C ratios, hyperchromatic nuclei, and scant cytoplasm. Depending on the subtypes, the sizes of lymphoma cells could vary markedly. Lymphoma cells tend to have more clumped chromatin than MCC cells. When cytomorphological differences are subtle, immunohistochemical study and/or flow cytometry are helpful in differentiation. However, some MCCs show positivity for TdT and CD10. Therefore, a multimarker panel is recommended.

High-grade urothelial carcinoma can have variable cytomorphological appearances, so it should always be considered in the differential diagnosis. About half of the MCCs show P63 positivity, mimicking urothelial carcinoma immunohistochemically.[4] Rare MCCs even show focal weak staining for GATA3.[5] However, strong and diffuse immunohistochemical positivity of GATA 3 and uroplakin and negativity for neuroendocrine markers favor the diagnosis of urothelial carcinoma.

In our case, in addition to the scattered tumor cells, the urine sample also showed marked mixed inflammation. For patients with bladder tumors, it is not uncommon to have concurrent infections. Effort should be made to avoid neglecting the rare tumor cells in the background of numerous inflammatory cells and reactive urothelial cells.

**BRIEF REVIEW OF THE TOPIC**

MCC, previously known as trabecular carcinoma/sweat gland carcinoma/Toker’s tumor, was first described in 1972 by Toker.[6] Later, Tang and Toker suggested that this tumor may develop from Merkel cells and therefore renamed it as MCC.[7] Although its exact origin is still unclear, MCC is currently considered as a highly aggressive cutaneous neuroendocrine tumor, with greater metastatic potential than malignant melanoma.[8] MCC is more common in males, with the most common primary site being head and neck. Heath et al.[9,10] suggested the mnemonic AEIOU for the clinical features of MCC. They are asymptomatic; expanding rapidly (doubling in <3 months); immune suppressed; older than 50 years; and UV exposed skin site, especially fair skin. The incidence of MCC in US was about 0.7 cases/100,000 people in 2013, and it is still rising.[11] The possible reasons for the rising incidence include identification of the association with Merkel cell polyomavirus (MCPyv); introduction of CK20 immunostain leading to increased detection rate; and increased aging population.[11] Although distant metastasis of MCC is common, urinary bladder is a very unusual site of MCC involvement and literature is limited to few case reports.[12-14]

The treatment for primary cutaneous MCC is surgery with optional sentinel lymph node biopsy and radiotherapy. Metastatic MCC has a bad prognosis. Recently, immunotherapy with PD-1 or PD-L1 inhibitors has been used to treat metastatic MCC. Avelumab, a PD-L1 inhibitor, is approved by FDA in 2017 for the treatment of metastatic MCC in adult and pediatric patients 12 years and older.[15]

**SUMMARY**

The presence of small round blue cell tumors in urine has a broad differential diagnosis, including but not limited to small cell carcinoma, lymphoma, and high-grade urothelial carcinoma. Metastatic MCC, although rare, should be considered in the differentials, especially if the patient is elderly with a history of skin MCC.

**COMPETING INTEREST STATEMENT BY ALL AUTHORS**

The authors declare that they have no competing interests.

**AUTHORSHIP STATEMENT BY ALL AUTHORS**

Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the
content of this article. All authors read and approved the final manuscript. Each author acknowledges that this final version was read and approved.

ETHICS STATEMENT BY ALL AUTHORS

As this is case without identifiers, our institution does not require approval from the Institutional Review Board (IRB) (or its equivalent).

LIST OF ABBREVIATIONS (In alphabetic order)

DLBCL – diffuse large B cell lymphoma
MCC– Merkel cell carcinoma
MCPyv – Merkel cell polyomavirus
SmCC – small cell carcinoma

EDITORIAL/PEER-REVIEW STATEMENT

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REFERENCES

1. Pelletier DJ, Czeczok TW, Bellizzi AM. A monoclonal antibody against SV40 large T antigen (PAb416) does not label Merkel cell carcinoma. Histopathology 2018;73:162-6.
2. Kervarrec T, Tallet A, Miquelestorena-Standley E, Houben R, Schrama D, Gambichler T, et al. Diagnostic accuracy of a panel of immunohistochemical and molecular markers to distinguish Merkel cell carcinoma from other neuroendocrine carcinomas. Mod Pathol 2019;32:499-510.
3. Wong HH, Wang J. Merkel cell carcinoma. Arch Pathol Lab Med 2010;134:1711-6.
4. Asioli S, Righi A, Volante M, Eusebi V, Bussolati G. p63 expression as a new prognostic marker in Merkel cell carcinoma. Cancer 2007;110:640-7.
5. Mertens RB, de Peralta-Venturina MN, Balzer BL, Frishberg DP. GATA3 expression in normal skin and in benign and malignant epidermal and cutaneous adnexal neoplasms. Am J Dermatopathol 2015;37:885-91.
6. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972;105:107-10.
7. Sun CC, Toker C, Masi JD, Elias EG. Primary low grade adenocarcinoma occurring in the inguinal region. Cancer 1979;44:340-5.
8. Grabowski J, Saltzstein SL, Sadler GR, Tahir Z, Blair S. A comparison of Merkel cell carcinoma and melanoma: Results from the California cancer registry. Clin Med Oncol 2008;2:327-33.
9. Schrama D, Becker JC. Merkel cell carcinoma--pathogenesis, clinical aspects and treatment. J Eur Acad Dermatol Venereol 2011;25:1121-9.
10. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Peñas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: The AEIOU features. J Am Acad Dermatol 2008;58:375-81.
11. Paulson KG, Park SY, Vandeven NA, Lachance K, Thomas H, Chapuis AG, et al. Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics. J Am Acad Dermatol 2018;78:457-63.
12. Santis WE, Billings EJ, DeWolf WC. Metastatic Merkel cell tumor to bladder presenting as an encroachment tumor with gross hematuria. Urology 1999;54:163.
13. Strasser H, Amann K, Schrott KM, Krause FS. Solitary metastasis of a Merkel cell tumor to the urinary bladder. Anticancer Res 2008;28:1361-4.
14. Mack DP, Moussa M, Cook A, Izawa JI. Metastatic Merkel cell tumor to the prostate and bladder. Urology 2004;64:156-8.
15. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/avelumab-bavencio. [Last accessed on 2020 Jun 25].

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