ACCSCIENCE PUBLISHING

Tumor Discovery

CASE REPORT

Signet ring cell carcinoma of the urinary bladder presenting with carcinocythemia and skeletal metastasis: A case report

Emma Rullo[1]*, Piergianni Biondi[2], Chiara Nicolazzo[3], Walter Gianni[2], Luciano Colangelo[2], Mirella Cilli[2], Paola Gazzaniga[3], Mara Riminucci[1], Alessandro Corsi[1], and Salvatore Minisola[2]

[1]Department of Molecular Medicine, Sapienza University, and Section of Pathology, Policlinico Umberto I, Rome, Italy

[2]Department of Clinical, Internal, Anesthesiologic and Cardiovascular Sciences, Sapienza University, and Mineral Metabolism Section, Policlinico Umberto I, Rome, Italy

[3]Department of Molecular Medicine, Sapienza University, and Cancer Liquid Biopsy Unit, Policlinico Umberto I, Rome, Italy

Abstract

Cancer of unknown primary accounts for approximately 3 – 5% of all malignancies and is typically associated with a dismal prognosis. We describe a 65-year-old man who presented with skeletal metastasis and circulating tumor cells exhibiting signet ring (SR) morphology. The patient was diagnosed with SR cell carcinoma (SRCC) through a bone marrow biopsy. This case report aimed to emphasize the importance of clinicians' awareness of SRCC of the urinary bladder. The primary site of tumor origin was not identified as *antemortem*. The patient died 2 months after being admitted for pulmonary embolism. At autopsy, the urinary bladder was determined to be the primary site of the tumor. Primary SRCC of the urinary bladder is extremely rare. There are currently no established consensus guidelines for its management. Surgery continues to be the primary treatment option when the condition is localized.

Keywords: Cancer of unknown primary; Signet ring cell carcinoma; Urinary bladder carcinoma; Carcinocythemia

***Corresponding author:**
Emma Rullo
(emma.rullo@uniroma1.it)

Citation: Rullo E, Biondi P, Nicolazzo C, *et al*. Signet ring cell carcinoma of the urinary bladder presenting with carcinocythemia and skeletal metastasis: A case report. *Tumor Discov*. doi: 10.36922/td.3736

Received: May 22, 2024

Accepted: August 7, 2024

Published Online: October 8, 2024

1. Introduction

Cancer of unknown primary (CUP) is defined by the European Society of Medical Oncology as a "carcinoma or undifferentiated neoplasm for which a standardized diagnostic workup fails to identify the primary tumor responsible for metastatic seeding."[1] It constitutes <5% of all cancers and its incidence is higher in men and increases with age.[1-4] Histologically, approximately 80% of the tumors are adenocarcinomas or undifferentiated carcinomas.[1-6] Typically, patients exhibit metastases in various organs, with the liver being the most frequently affected site.[1-4]

In the urinary bladder, primary adenocarcinomas account for <2% of all primary malignant tumors.[7] Pure signet ring cell carcinoma (SRCC) is one of the rarest histological subtypes and is associated with the worst prognosis because of its presentation at an advanced stage and possible intrinsic aggressive biological features.[7-10]

Adenocarcinomas are the most prevalent histologic type that manifests as CUP. SRCC, a poorly differentiated aggressive subtype of adenocarcinoma, has been rarely reported to manifest as metastatic SRCC of unknown primary origin.[11] This case report describes a patient who presented with skeletal metastasis and circulating tumor cells (CTCs) exhibiting signet ring (SR) morphology. The diagnosis of SRCC was confirmed through bone marrow biopsy results. Despite an in-depth diagnostic workup, we were unable to establish the primary site of the tumor. The patient died 2 months after hospitalization. At autopsy, the urinary bladder was established as the primary site of the tumor.

2. Case presentation

A 65-year-old man was admitted for severe asthenia and low-grade fever. He reported having previously undergone mandibular surgery for ameloblastoma. Blood tests revealed severe anemia (Hemoglobin = 3.8 g/dL), thrombocytopenia (34.000/mm^3), high ferritin (2100 ng/mL) and lactate dehydrogenase levels (777 U/L), hypokalemia (1.61 mEq/L), hypoproteinemia, and normal liver enzymes and tumor markers. Serum alkaline phosphatase levels were elevated (1102 U/L, n.v. 34 – 102 U/L). Tc-99m-methylene-diphosphonate scintigraphy revealed a super-scan pattern (i.e., there was a concentration of the radiotracer in the skeleton with minimal or no activity in the soft tissues or urinary tract) with multiple foci of increased tracer uptake throughout the skeleton (Figure 1A). Whole-body computed tomography (CT) revealed mixed (lytic and sclerotic) vertebral lesions (Figure 1B), indicating metastatic skeletal disease. The free/total prostate-specific antigen (PSA) ratio was 9.41. The FDA-approved CellSearch® system (Menarini Silicon Biosystems, Castel Maggiore, Bo, Italy) detected 387 solitary and 9 clustered (2 – 3 cells) cytokeratin (CK)-positive CTCs with SR morphology (Figure 2A), as previously described.[12] Briefly, 7.5 mL of whole blood was processed using the CellSearch® CTC kit. After EpCAM-based immunomagnetic capture, the cells were stained with antibodies anti-CK8,18,19-fluorescein isothiocyanate and anti-CD45-allophycocyanin and with 4′,6-diamidino-2-phenylindole for detecting the nucleus. Immunofluorescence images were eventually analyzed using CellSearch® Analyzer II. SRCC metastasis was diagnosed on the iliac crest and vertebral biopsies (Figure 2B and C). The neoplastic cells tested negative for CK7, CK20, TTF1, and PSA. Because SRCC is known to originate more frequently from the gastrointestinal tract, esophagogastroduodenoscopy, colonoscopy, small-intestine contrast ultrasonography, and CT enterography revealed negative results. Transrectal ultrasonography and urinary cytology also revealed

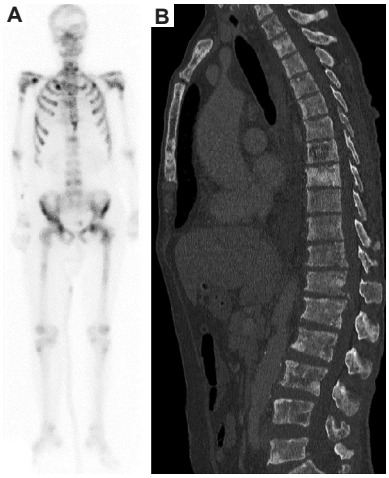

Figure 1. Findings of skeletal involvement (A) Tc-99m-methylene-diphosphonate scintigraphy revealing a super-scan pattern with multiple foci of increased tracer uptake throughout the skeleton, with little or no activity in the soft tissues or urinary tract. (B) Computed tomography (sagittal plane) image revealing mixed (lytic and sclerotic) lesions in the vertebral bodies.

negative results. Two peripheral lesions indeterminate for malignancy were identified during multiparametric prostate-magnetic resonance imaging, which was conducted in response to the low free/total PSA ratio and the negative results of the immunohistochemical staining for CK7 and CK20.[1,3-6] Prostatic biopsy was planned but not performed because of the rapid deterioration of the patient's general conditions (Eastern Cooperative Oncology Group/World Health Organization Performance Status 4). Androgen deprivation therapy and zoledronate were initiated, but the patient died suddenly. An autopsy revealed pulmonary embolism as the cause of death. The entire prostate was processed for histological examination due to the clinical suspicion of prostate cancer; however, it was revealed to be malignancy-free. The urinary bladder was devoid of any intraluminal mass. Histological examination revealed diffuse SRCC cell infiltration within the entire thickness of the lamina propria (Figure 2D and E). Rare cells were immunoreactive for CK7 and CK20. Neoplastic lymphatic invasion within the urinary bladder wall was significant. Mesenteric lymph nodes had metastases along the vertebrae.

3. Discussion

The case reported here represents a typical example of CUP, in which an extensive diagnostic workup failed to establish the tumor's primary origin. CUP, a well-established oncologic condition, is associated with a dismal outcome and a median survival duration of 8 – 11 months.[1-4] Its diagnosis is always based on the histopathologic examination of the biopsy specimen

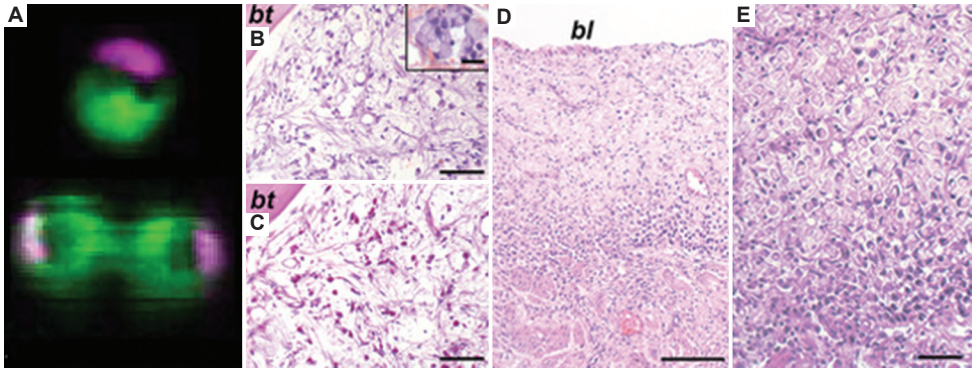

Figure 2. Representative images of a single (top) circulating tumor cell (CTC) and a cluster of two (bottom) CTCs exhibiting small signet ring (SR) morphology (cytokeratin/4′,6-diamidino-2-phenylindole) are shown in panel (A). (B and C) Consecutive sections of the bone marrow biopsy stained with hematoxylin–eosin and periodic acid–Schiff are shown in panels (B) and (C), respectively. The insert in B shows a cluster of SR cells. These cells are promptly recognizable for the eccentrically located nucleus and the abundant amount of mucin within the cytoplasm. Representative low- and high-power magnification of the urinary bladder wall stained with hematoxylin–eosin are shown in panels (D) and (E), respectively. The whole thickness of the lamina propria is diffusely infiltrated by neoplastic cells with SR morphology.
Abbreviations: *bt* (in B and C) is for bone trabecula and *bl*, *lp*, and *mp* (in D) are for urinary bladder lumen, lamina propria, and muscularis propria, respectively. Magnification for A: 10 ×. Scale bars: 100 mm for B-D and 80 mm for E.

from a metastatic site.[3] Immunostaining for CK7 and CK20 is typically performed when adenocarcinoma is detected histopathologically, providing physicians with indications of the tumor's primary site. CK7 is widely expressed in the breast, lung, pancreas, biliary tract, and transitional carcinomas, whereas CK20 is expressed in the gastrointestinal tract (especially colon and rectum) and transitional carcinomas.[1,3-6] In our patient, results for the CKs, TTF1, and PSA were negative on sections from the bone marrow biopsy specimen.

Despite extensive clinical workup, a primary tumor is identified in <20% of patients with CUP. *Antemortem* and autopsy studies have reported that 70% of cases remain undiagnosed.[4] Autopsy enabled us to identify the urinary bladder as the primary site of the tumor's origin. The urinary bladder is not among the most frequently encountered sites of the primary tumor, which typically include the pancreas (20 – 26%), lungs (17 – 23%), colon/rectum (4 – 10%), liver (3 – 11%), stomach (3 – 8%), kidneys (4 – 6%), ovaries (3 – 4%), prostate (3 – 4%), and breast (2%).[3,4] In our case, the issue was further complicated by the histological type of the diagnosed tumor. SRCC most commonly originates in the gastrointestinal tract and, in the genitourinary system, it rarely occurs in the prostate[7] and urinary bladder, where it accounts for no more than 0.6% of all primary malignant tumors.[8-10] Recent reviews on primary SRCC of the urinary bladder have indicated that approximately 300 cases have been reported in the English literature.[8-10] The carcinoma commonly arises in men in their seventh decade of life, typically at an advanced tumor stage, and exhibits an aggressive clinical course with a high frequency of metastasis and an ominous prognosis.[8-10] Its clinical presentation is comparable to that of the more common urothelial carcinoma of the urinary bladder, and hematuria is its most prevalent presenting symptom.[8-10] Imaging features are not specific, and SRCCs have been identified in only urine samples rarely.[13] Notably, the manifestation of SRCC as CUP has been rarely reported.[11] In our patient, SRCC manifested with skeletal metastasis and carcinocythemia (i.e., blood circulating cells from solid epithelial tumors), which indicated an advanced tumor stage, and the tumor's site of origin was determined during autopsy. Carcinocythemia, first described by Carey *et al.*,[14] is a rare finding that is reportedly becoming more common.[15] To the best of our knowledge, carcinocythemia has never been associated with primary urinary bladder SRCC.

In cases such as the one reported here, a comprehensive diagnostic workup is necessary to identify the primary site of malignancy and determine the best therapeutic options to improve the prognosis. However, due to the rarity of primary urinary bladder SRCC, there are no established consensus guidelines for its management.[8-10] The localized form is treated primarily with surgery, and the prognosis is favorable when the tumor is detected early and removed through radical resection.[10] Diverse treatment approaches involving surgery, radiotherapy, chemotherapy, and their combinations for both localized and metastatic urinary bladder SRCC have been recently reviewed.[8] As indicated by Lendorf *et al.*,[8] exploring the role of immune checkpoint inhibitors may represent a valuable area for future clinicopathological research in the context of primary urinary bladder SRCC. However, because modern therapeutic approaches tend to be limited

to the primary site of origin of a malignant tumor[2] and molecular approaches that could be useful to this goal are not always accessible,[16,17] the application of deep-learning-based algorithms on whole-slide histological images[18] is a promising tool for identifying the primary site of origin of a CUP.

4. Conclusion

Primary SRCC is a variant of adenocarcinoma that rarely develops primarily in the urinary bladder. It may manifest as a CUP, as evidenced by the case described here. The prognosis of this carcinoma is typically dismal as it is an aggressive tumor, and the diagnosis is generally made at an advanced stage of the disease. The urinary bladder should be considered as a site of origin of SRCC when the most common sites of origin (i.e., the gastrointestinal tract) have been excluded, even in the absence of an endoluminal mass and with negative urinary cytology results, as observed in the case reported here. We believe that our case may have significant implications in clinical practice. It is imperative that clinicians are aware of the possibility of a metastatic SRCC originating from the urinary bladder.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Emma Rullo, Mara Riminucci, Alessandro Corsi, Salvatore Minisola

Formal analysis: Emma Rullo, Piergianni Biondi, Chiara Nicolazzo, Walter Gianni, Luciano Colangelo, Mirella Cilli, Paola Gazzaniga, Mara Riminucci, Alessandro Corsi

Methodology: Emma Rullo, Chiara Nicolazzo, Paola Gazzaniga, Mara Riminucci, Alessandro Corsi

Investigation: Emma Rullo, Chiara Nicolazzo, Paola Gazzaniga, Mara Riminucci, Alessandro Corsi, Salvatore Minisola

Writing–original draft: Emma Rullo

Writing–review & editing: Emma Rullo, Mara Riminucci, Alessandro Corsi, Salvatore Minisola

Ethics approval and consent to participate

Ethical approval is not required as this is a case report. All the clinical and pathologic investigations detailed in the manuscript have been conducted in accordance with the Declaration of Helsinki and its later amendments.

Consent for publication

Informed consent for the publication of data and images was obtained from the next-of-kin as the subject had passed away.

Availability of data

All data generated or analyzed during this study are included in the submitted article.

References

1. Krämer A, Bochtler T, Pauli C, *et al*. Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(3):228-246.

   doi: 10.1016/j.annonc.2022.11.013

2. Levi F, Te VC, Erler G, Randimbison L, La Vecchia C. Epidemiology of unknown primary tumours. *Eur J Cancer*. 2002;38(13):1810-1812.

   doi: 10.1016/s0959-8049(02)00135-1

3. Massard C, Loriot Y, Fizazi K. Carcinomas of an unknown primary origin--diagnosis and treatment. *Nat Rev Clin Oncol*. 2011;8(12):701-710.

   doi: 10.1038/nrclinonc.2011.158

4. Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). *Crit Rev Oncol Hematol*. 2009;69(3):271-278.

   doi: 10.1016/j.critrevonc.2008.09.005

5. Oien KA. Pathologic evaluation of unknown primary cancer. *Semin Oncol*. 2009;36(1):8-37.

   doi: 10.1053/j.seminoncol.2008.10.009

6. Beauchamp K, Moran B, O'Brien T, *et al*. Carcinoma of unknown primary (CUP): An update for histopathologists. *Cancer Metastasis Rev*. 2023;42:1189-1200.

   doi: 10.1007/s10555-023-10101-6

7. Celik O, Budak S, Ekin G, Akarken I, Ilbey YO. A case with primary signet ring cell adenocarcinoma of the prostate and review of the literature. *Arch Ital Urol Androl*. 2014;86(2):148-149.

   doi: 10.4081/aiua.2014.2.148

8. Lendorf ME, Dohn LH, Dunga BA, Loya AC, Pappot H. An updated review on primary signet-ring cell carcinoma of the urinary bladder and report of a case. *Scand J Urol*. 2018;52(2):87-93.

   doi: 10.1080/21681805.2017.1418020

9. Benerjee N, Parmar K, Vaiphei K. Primary signet-ring cell carcinoma of the urinary bladder. *Autops Case Rep*. 2021;11:e2021264.

doi: 10.4322/acr.2021.264

10. Ivanov A, Antonov P, Zapryanov M, Uchikov P, Belovezhdov V. Primary signet-ring cell adenocarcinoma of the bladder-A case report and review of literature. *Urol Case Rep*. 2022;42:102022.

    doi: 10.1016/j.eucr.2022.102022

11. Bagaporo Larrazabal R Jr., Cheng PVC, David-Wang A, Requiso D. Signet-ring cell adenocarcinoma of unknown primary presenting with superior vena cava (SVC) syndrome: Rare type of cancer. *BMJ Case Rep*. 2019;12(12):e232269.

    doi: 10.1136/bcr-2019-232269

12. Nicolazzo C, Raimondi C, Gradilone A, *et al*. Circulating tumor cells in right- and left-sided colorectal cancer. *Cancers* (*Basel*). 2019;11(8):1042.

    doi: 10.3390/cancers11081042

13. DeMay RM, Grathwohl MA. Signet-ring-cell (colloid) carcinoma of the urinary bladder. Cytologic, histologic and ultrastructural findings in one case. *Acta Cytol*. 1985;29(2):132-136.

14. Carey RW, Taft PD, Bennett JM, Kaufman S. Carcinocythemia (carcinoma cell leukemia). An acute leukemia-like picture due to metastatic carcinoma cells. *Am J Med*. 1976;60(2):273-278.

    doi: 10.1016/0002-9343(76)90437-x

15. Ronen S, Kroft SH, Olteanu H, Hosking PR, Harrington AM. Carcinocythemia: A rare entity becoming more common? A 3-year, single institution series of seven cases and literature review. *Int J Lab Hematol*. 2019;41(1):69-79.

    doi: 10.1111/ijlh.12924

16. Krawczyk P, Jassem J, Wojas-Krawczyk K, Krzakowski M, Dziadziuszko R, Olszewski W. New genetic technologies in diagnosis and treatment of cancer of unknown primary. *Cancers* (*Basel*). 2022;14(14):3429.

    doi: 10.3390/cancers14143429

17. Hayashi H, Takiguchi Y, Minami H, *et al*. Site-specific and targeted therapy based on molecular profiling by next-generation sequencing for cancer of unknown primary site: A nonrandomized phase 2 clinical trial. *JAMA Oncol*. 2020;6(12):1931-1938.

    doi: 10.1001/jamaoncol.2020.4643

18. Lu MY, Chen TY, Williamson DFK, *et al*. AI-based pathology predicts origins for cancers of unknown primary. *Nature*. 2021;594(7861):106-110.

    doi: 10.1038/s41586-021-03512-4