JMRO

Journal of Medical and Radiation Oncology

Journal homepage: www.jmedradonc.org

High-Grade Urothelial Carcinoma with Squamous Differentiation and Favourable Response to Immunotherapy – a Case Report

Alecsandra Gorzo[1], Diana Galos[1], Daniel Sur[1,2,], Ramona Matei[3]

[1] *Department of Medical Oncology, "Ion Chiricuță" Oncology Institute, Cluj-Napoca, Romania*
[2] *11th Department of Medical Oncology, University of Medicine and Pharmacy, "Iuliu Hațieganu" Cluj-Napoca, Romania*
[3] *Municipal Clinical Hospital, Cluj-Napoca, Romania*

Corresponding author: Daniel Sur; **e-mail**: dr.geni@yahoo.co.uk

Abstract

Bladder cancer is the 10th most common cancer type worldwide, with a median age of diagnostic of 75 years. Male sex, white race, personal history of pelvic radiation, and tobacco use are considered risk factors. Urothelial carcinoma (UC) is the most frequent histology. Squamous differentiation (SD) is the most common histologic variant in bladder cancer (20% of cases) and is associated with a worse prognosis. We presented the case of a 75-years old male patient diagnosed with high-grade (G3) UC of the bladder with SD who developed skin metastasis shortly after completing the adjuvant chemotherapy. He was started on immunotherapy with Atezolizumab, with good response until this report was written (for twelve months).

Keywords: *bladder cancer, squamous differentiation, skin metastasis, immunotherapy*

Clinical Case Reports

1. Introduction

Bladder cancer (BC) carries a significant social burden, with up to 550,000 cases diagnosed every year worldwide and a median age of diagnostic of 75 years (1). Tobacco use is the most common risk factor and contributes to the increasing incidence of BC in Western countries. Male sex, white race, personal history of pelvic radiationare also considered risk factors (2). BC represents a spectrum of diseases which include non-muscle-invasive disease (NMIBC), muscle-invasive disease (MIBC), and advanced or metastatic disease (3). Urothelial carcinoma (UC) is the predominant histological subtype in Europe and the United States (90%). UC with squamous differentiation (SD) is the most common histologic variant in BC (20% of cases), and it was associated with a poor

https://doi.org/10.53011/JMRO.2022.01.07
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prognosis (4).We presented a case of ahigh-grade(G3) UC with SD and with favourable response to immunotherapy.

2. Case Report

A 75-year-old male patient presented to our unit with a recent diagnosis of BC. The patient has a medical history of hypertension and type 2 diabetes. He did not report tobacco or alcohol use.

At the end of January 2020, the patient presented to another urology department with hematuria. A CT-urography revealed a bladder tumor measuring 45/30 mm that involved the left ureteral orifice and hydronephrosis grade 4 in the left kidney, with no abdominal or pelvic lymph nodes. Further, the patient underwent transurethral resection for bladder tumor (TURBT), in February 2020. The pathology report described a high-grade (G3) papillary UC, pT2 - MIBC. Soon after the diagnosis, at the beginning of March 2020, the patient presented to our emergency department with gross hematuria and clots. He was admitted to the urology department and stabilized. During admission, a cystoscopy was performed, which excluded an early relapse. Moreover, a CT scan of the thorax to complete the staging evaluation showed no signs of metastatic lesions. The case was further discussed in our multidisciplinary team, and the final diagnostic was of high-grade (G3) UC of the bladder T2N0M0, stage II, according to the AJCC 8th edition. Based on the stage, patient's fitness, and informed consent, the therapeutic strategy consisted of neoadjuvant chemotherapy followed by radical cystectomy. Considering the worldwide health crisis caused by the COVID-19 pandemic, which spread quickly to our country, we decided to start the treatment as soon as possible. Therefore, from March 2020 to May 2020, the patients received three cycles of neoadjuvant chemotherapy based on carboplatin AUC5 and gemcitabine 1000 mg/m2. After completing the three cycles, the CT scan described the bladder having diffuse wall thickening (12 mm) and multiple diverticula, hydronephrosis grade 2/3 in the left kidney, and iliac lymph nodes measuring about 8-10 mm in short axis diameter. (Fig. 1).

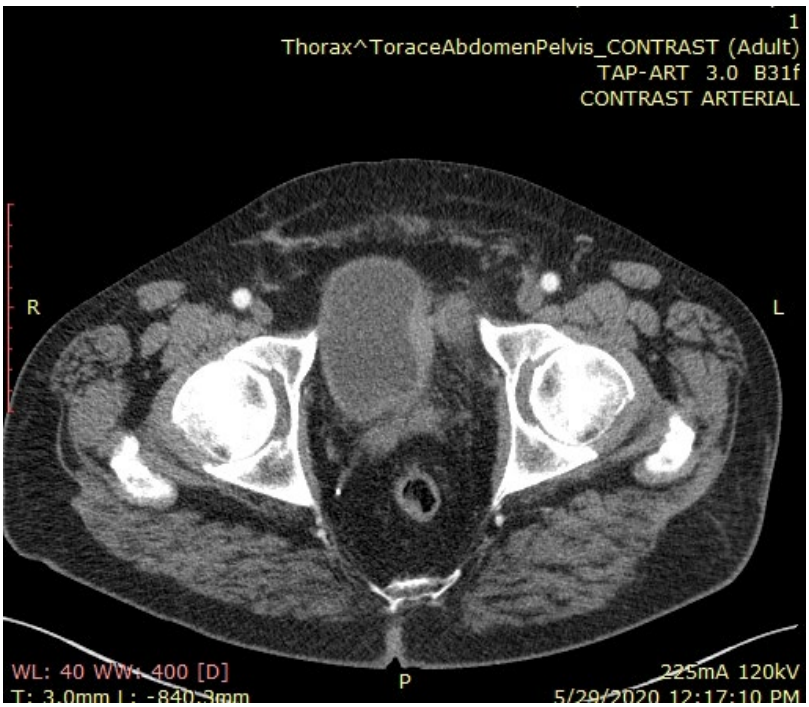

Fig.1: CT scan after neoadjuvant chemotherapy

Consequently, in June 2020, the patients underwent cystoprostatectomy, and the pathology report revealed a high-grade UC (G3) with SD (20%) ypT3aN1MxL1VoPnoRo. Considering the poor prognostic factors (squamous differentiation, residual disease after neoadjuvant therapy, lymphovascular invasion), we decided to complete the therapeutic sequence with adjuvant chemotherapy. Therefore, from August 2020 to October 2020, the patients received three additional cycles of adjuvant chemotherapy with carboplatin AUC5 and gemcitabine 1000 mg/m^2.

Shortly after completing the treatment, in December 2020, the patient presented with indurated skin nodules in the hypogastrium at the surgical incision site. The lesions were interpreted as skin metastasis (Fig. 2).

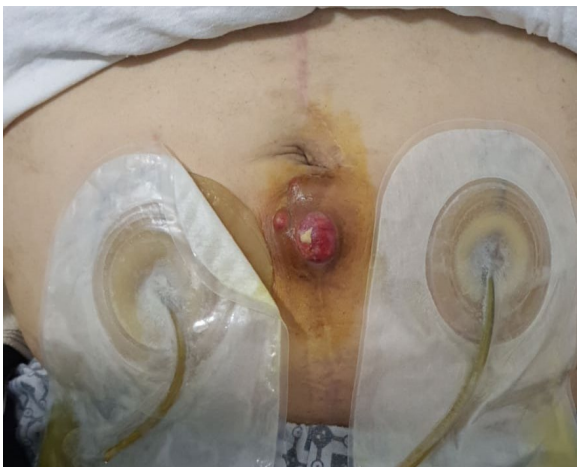

Fig. 2: Erythematous, indurated skin nodules in the hypogastrium

A CT scan confirmed the recurrence. The results showed a soft tissue mass in the lower anterior abdominal wall measuring 3/4 cm and another with similar characteristics in the lower right anterolateral wall. Moreover, the CT scan showed a left iliac lymphadenopathy measuring 3.5/2 cm and peritoneal carcinomatosis. Considering the available treatment options, from January 2021, the patient was started on immunotherapy with Atezolizumab 1200mg IV every 3 weeks. The first follow-up CT scan was performed after three months, in March 2021 and pelvic lymph nodes measured less than 10mm in diameter. The patient maintained a good performance status (IP ECOG 1), no adverse events were reported throughout treatment, and the skin nodules were considerably reduced in size (Fig. 3).

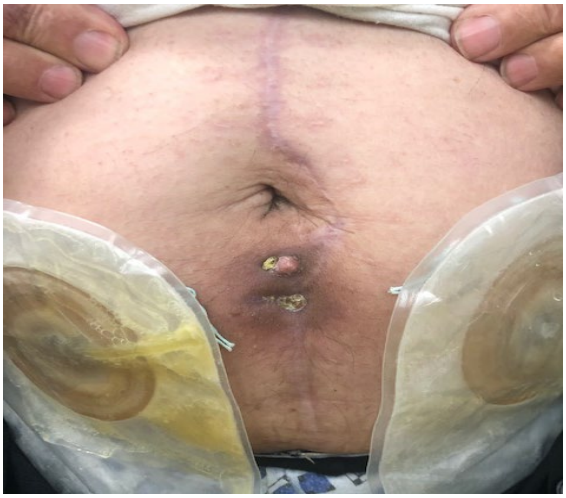

Fig. 3: Clinical assessment after three months of immunotherapy- skin nodules reduced in size

Systemic therapy was maintained with Atezolizumab 1200 mg IV 3 weeks. Subsequent clinical and imagistic follow-up showed overall improvements, and the systemic immunotherapy was continued until this report was written (Fig.4).

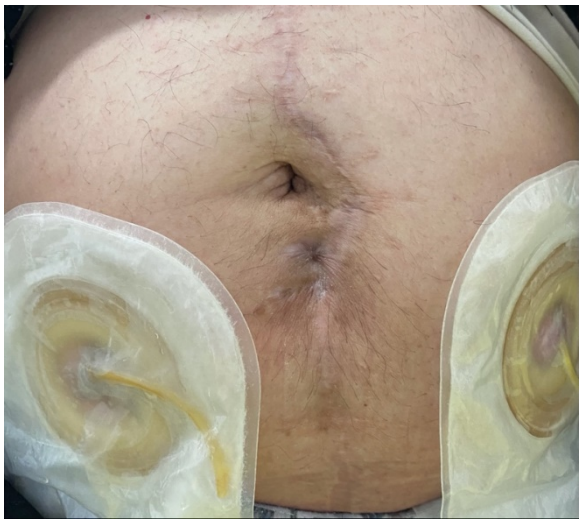

Fig. 4: Clinical assessment from December 2021

3. Discussion

UC is the most common tumor type of the urinary tract and has a propensity for divergent differentiation. Squamous differentiation occurs in about 20% of cases and is characterized by intracellular bridges of keratinization (5). This histological variant was associated with more advanced stages, shorter disease-free survival (DFS), and a higher recurrence rate (RR) (6). As regards our case, recurrence was diagnosed very shortly after completing the adjuvant sequence, after only two months. In terms of overall survival (OS), the data are inconsistent. However, SD did not significantly influence OS in a recent meta-analysis investigating its prognostic value (7).

BC represents a spectrum of diseases which NMIBC, MIBC, and metastatic disease (8). The most common metastatic sites are regional lymph nodes, lung, liver, and bone. Skin metastasis is a rarity, with a handful of cases reported in the literature till now. The overall incidence of cutaneous metastasis is about 5% for all malignancies and 0.8% for BC (9). Skin infiltration by cancerous cells can occur through several routes, including lymphatic, hematologic, iatrogenic implantation, or direct tumor invasion. In our case, iatrogenic implantation following an extensive surgery like cystoprostatectomy could the underlying mechanism leading to skin metastasis. Moreover, the lesions can mimic other dermatological conditions like melanoma or sarcoma (10).

The treatment of BC was almost unchanged during the last three decades. BC was one of the most underfunded among the common cancer types in the early 2000s, which limited the understanding of tumor biology and led to inadequate treatment progress (11). The mixed histologies, including SD, are usually treated in the same manner as pure UC. On the other hand, pure squamous cell carcinoma and adenocarcinoma were not proven to benefit from neoadjuvant/adjuvant chemotherapy.Our patient presented with the diagnostic of MIBC, for which the standard of care consists of radical cystectomy. The high RR following radical cystectomy alone pointed to the use of neoadjuvant chemotherapy (cisplatin-based regimens) (12). However, our patient presented with kidney function impairment (creatinine clearance-43 ml/ min/ 1.73mp), and therefore cisplatin was replaced with carboplatin.The role of adjuvant chemotherapy remains a matter of debate, especially in patients who previously received neoadjuvant chemotherapy. Adequately powered randomized control trials did not fully establish its' role (13). Though, observational studies reported a survival benefit associated with adjuvant chemotherapy after neoadjuvant treatment and radical cystectomy, especially in patients with adverse pathologic features (pT3/ T4 and/or pN+) (14). Therefore, considering the poor prognostic factors after radical cystectomy (squamous differentiation, residual disease after neoadjuvant therapy, lymphovascular invasion), we proposed three cycles of adjuvant chemotherapy to our patient.

As regards the metastatic setting, an initial cisplatin-based regimen is the preferred treatment option (15). In 2016, atezolizumab (a PD-L1 inhibitor) was the first new drug approved by the FDA in more than 20 years to treat advanced/metastatic UC who progressed after platinum-based chemotherapy (16). However, in the long-term analysis of the phase III IMvigor211 trial, atezolizumab did not confer an OS benefit compared to chemotherapy in prior-platinum-treated advanced/metastatic UC patients. Consequently, these results led to the withdrawal of atezolizumab for this indication as second-line therapy in the United States.Currently, there are five immune checkpoint inhibitors (ICIs) approved for the treatment of advanced UC (atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab) (17). Recently, atezolizumab and pembrolizumab received approval as first line in cisplatin-ineligible patients with advanced UC (18).The clinical efficacy of ICIs in tumors with predominant or pure variant histologies was poorly understood, as these categories were kept out from clinical trials. Recent studies brought light into the subject and showed that histological variants, including squamous differentiation, have comparable rates of PD-L1 expression with those found in urothelial tumors. These findings suggest that histological variants could benefit from ICIs as much as pure UC.

Metastatic bladder cancer has a poor prognosis with a 5-year OS of 5%. Moreover, skin metastasis from a primary UC is associated with a median OS of less than a year (19). Our patient received immunotherapy for twelve months with no sign of disease progression and no adverse events reported. (Fig. 4)

4. Conclusion

The occurrence of UC with SD is rare and may reflect a poor outcome. Therefore, it is essential to diagnose the histological variants correctly to determine the optimal treatment and predict the patient's prognostic.

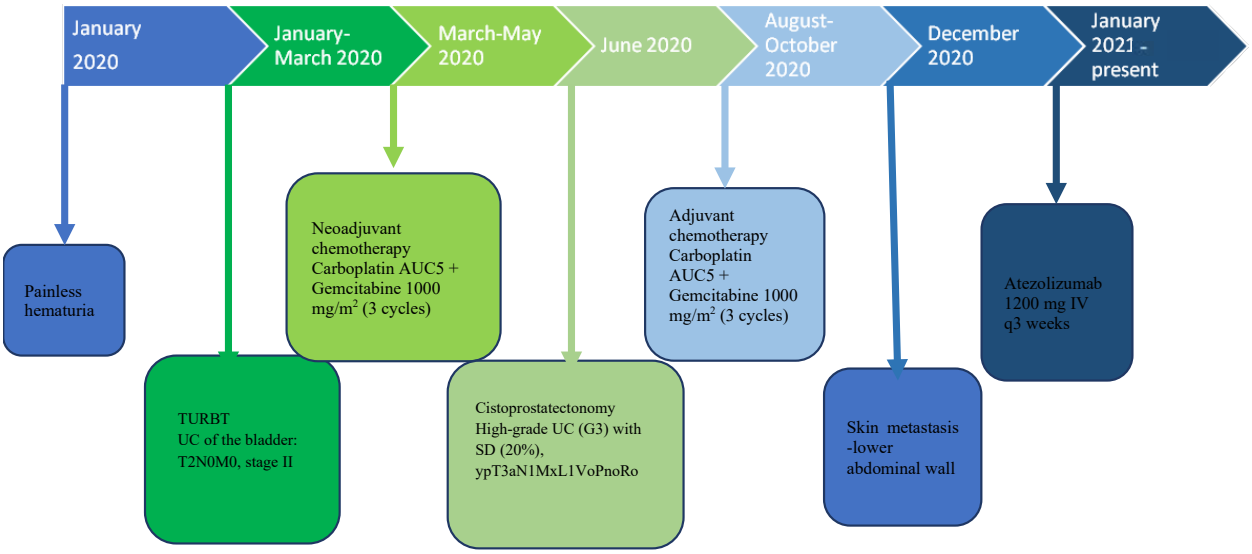

Fig. 4: The patient's disease progression and treatment options

Abbreviations:
BC - bladder cancer
DFS - disease-free survival
FDA - Food and Drug Association
ICIs - immune checkpoint inhibitors
MIBC - muscle-invasive bladder cancer
NMIBC - non-muscle invasive bladder cancer
OS - overall survival
RR - response rate
SD - squamous differentiation
TURBT - transurethral resection for bladder tumor
UC - urothelial carcinoma

Statements:
Authors' contributions: All co-authors equally contributed to the manuscript.
Consent for publication: As the corresponding author, I confirm that the manuscript has been read and approved for submission by all co-authors.
Conflict of interest: All authors declare having no competing interests associated with this publication.
Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.
Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

Ethical Approval: The treatment strategy was approved by the „Institute of Oncology Cluj-Napoca" tumor board.

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