Metastatic Clinically-Aggressive Non-Invasive Low-Grade Urothelial Carcinoma Arising Post Autologous Transplant - Case Report and Review of the Literature

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Abstract

Background: Non-invasive low-grade urothelial carcinoma (UC) carries a very low risk of distant metastasis and such tumors are typically managed with localized therapies. These tumors also appear to be biologically distinct from high-grade invasive urothelial carcinoma, with unique molecular signatures and driver mutations. The efficacy of systemic therapy including platinum-based chemotherapy, immune checkpoint inhibitors (CPI), and FGFR blocking agents in non-invasive low-grade tumors has not been assessed.

Results: A 68-year-old woman with history of high-dose chemotherapy followed by autologous stem cell transplant (SCT) for treatment of breast cancer developed a renal mass 22 years later. She underwent a left nephroureterectomy, which revealed non-invasive low-grade UC (pT1a). Surveillance cystoscopy after 21 months showed non-invasive low-grade UC of the bladder. Shortly thereafter, she was discovered to have bilateral “cannon-ball” pulmonary metastasis and mediastinal lymphadenopathy, with biopsy of a lung lesion demonstrating metastatic low-grade UC. Foundation Medicine next generation sequencing (NGS) demonstrated an FGFR3 S249C mutation. She was treated with platinum-based chemotherapy, achieving a partial treatment response. She was subsequently initiated on CPI, but developed rapid disease progression in the lungs and new bony metastasis, with a bone biopsy confirming metastatic low-grade UC. She then rapidly deteriorated and passed away.

Conclusion: We report a unique case of clinically-aggressive metastatic non-invasive low-grade UC arising in a patient post autologous SCT. Molecular tumor profiling in this rare setting is crucial to assist with optimal selection of systemic therapy.

Introduction

SCT is associated with increased risk of secondary tumors, including UC [1,2]. Non-muscle-invasive bladder cancer (NMIBC) comprises tumors invading subepithelial connective tissue (T1), carcinoma in situ (CIS) and papillary (Ta), with identical staging for renal pelvis tumors. NMIBC has a 50-70% superficial recurrence risk and 5% of patients develop invasive disease [3]. Distant metastasis are extremely uncommon, particularly with low-grade solitary Ta tumors ≤ 3 cm in size, with less than 30 cases reported in literature [3,4]. These tumors are classified as low-risk [5]. Adjuvant therapy following transurethral bladder tumor resection includes a single-
dose of intravesicular chemotherapy, while similar upper tract tumors are managed with endoscopic resection or nephroureterectomy depending on tumor size with local chemotherapy installation [5]. We report a case of metastatic clinically-aggressive non-invasive low-grade UC arising in a patient with history of autologous SCT.

Case Report

A 68-year-old woman with history of stage III breast cancer treated with mastectomy, adjuvant radiation, high-dose chemotherapy and autologous SCT developed a renal mass 22 years later. She underwent left nephroureterectomy, which revealed a 2.5 cm low-grade pTa UC of the renal pelvis (Figure 1A). Surveillance cystoscopy after 21 months showed low-grade pTa UC of the bladder. Abdominopelvic MRI demonstrated new pulmonary masses. CT chest showed “cannon-ball” metastasis measuring up to 7.8 x 4.7 cm and mediastinal lymphadenopathy (Figure 2). Pulmonary lesion biopsy showed metastatic low-grade UC (Figure 1B). Foundation Medicine NGS of the lung biopsy specimen revealed PD-L1 CPS of 0, tumor mutational burden (TMB) of 0 m/Mb, stable microsatellite instability (MSI) status, and an FGFR3 S249C mutation. Clinically, she rapidly deteriorated with severe dyspnea requiring continuous supplemental oxygen, inability to walk more than several steps due to hypoxia, and an Eastern Cooperative Group (ECOG) performance status of 3.

She initiated palliative chemotherapy with carboplatin AUC 4 and gemcitabine 1,000 mg/m2 in 21-day cycles, ultimately completing 6 treatment cycles. Restaging imaging showed partial response and she experienced dramatic clinical improvement, with resolution of dyspnea and improvement of ECOG performance status to 1. Maintenance pembrolizumab 200 mg in 21-day cycles was initiated, but restaging imaging after 6 treatment cycles demonstrated new pulmonary masses and multiple bony lesions. After developing severe mid-back pain, a pathologic T9 fracture with epidural tumor extension was identified and treated with palliative radiation. Subsequently, a non-tramatic pathologic humerus fracture occurred, requiring surgical fixation. Bone biopsy from that procedure again revealed low-grade UC (Figure 1C). Post-operatively, she developed sepsis and respiratory failure, causing death.

Discussion

Low metastatic risk of NMIBC likely arises from lack of blood and lymphatic vessels within bladder submucosa [3]. One hypothesis regarding metastasis etiology postulates iatrogenic dissemination after lamina propria disruption during tumor resection or intravesicular therapy [3]. Another hypothesis involves missing high-grade or invasive tumor components with incomplete tumor resection or inaccurate pathologic evaluation [3]. All tumor samples in our case, including renal and bladder primaries as well as metastatic sites, demonstrated low-grade UC. This tumor exhibited extremely aggressive behavior, which may have stemmed from a previous SCT. Incidence of solid secondary tumors after SCT increases over time [1]. In a retrospective series of 1347 patients, solid tumor incidence was 2.54%, 6.79% and 9.14% at 5, 10 and 15 years, respectively [2]. Tumor types included
lung (14%), gastrointestinal (14%), skin (14%), breast (12%), head and neck (7.7%), and bladder (7.7%). In the general population, bladder cancer represented 4.5% of all new cancer cases in 2020 [4]. Multiple factors affect secondary tumor risk, including patient-related (i.e., age), primary disease-related (i.e., disease type, pre-SCT therapies), SCT-related (i.e., type and intensity of conditioning regimen, stem cell source, development of graft-versus-host disease), and non-SCT-related (i.e., germline genetic susceptibility, oncogenic viruses, lifestyle factors) [1]. Following SCT, a period of lymphopenia and cell-mediated antibody production, T- and natural killer cells occurs, leading to reduced immune surveillance of neoplastic cells [1]. DNA-damaging effects of cytotoxic chemotherapy and radiation used pre-SCT or in conditioning regimens also contribute to secondary tumors [1].

Low-grade NMIBC is molecularly distinct from high-grade invasive UC and demonstrates highly-conserved acquired activating mutations of the FGFR3, PIK3CA, STAG2, or RTK/RAS/RAF pathway [6,7]. Nearly 20% of advanced UC also harbors FGFR alterations, which are even more frequent (37%) in upper tract tumors [8]. Tumors with FGFR alterations are more likely to be “immunologically cold” and exhibit decreased clinical responses to immune checkpoint inhibitors [8]. This was seen in our case, where molecular predictive biomarkers associated with responses to CPI such as PD-L1, TMB, and MSI were low or stable on NGS. Indeed, our patient quickly progressed on pembrolizumab. Pan-FGFR inhibitor, erdafitinib, is approved in patients with advanced pretreated UC harboring FGFR alterations, but it wasn’t yet available in our case. Clinical trials evaluating the role of combination therapy with CPI and pan-FGFR inhibitors in metastatic UC harboring FGFR alterations are ongoing (NCT04003610). Given this unusual presentation, tumor profiling for targetable driver mutations is warranted.

Conclusion

Non-invasive low-grade UC rarely causes distant metastasis or leads to an aggressive clinical course. Host factors including prior autologous SCT may have influenced development of this rare presentation. Given the lack of standard-of-care therapies for this disease entity, obtaining NGS is warranted to help guide clinical management. Further research into the molecular basis of these tumors may illuminate additional treatment opportunities.

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Conflict-of-Interest: None

References


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