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Case Report

Metastatic Esophageal Adenocarcinoma to the Urinary Bladder During Immunotherapy: A Rare Case Report

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Abstract:

Metastatic Esophageal adenocarcinoma to the urinary bladder is extremely rare, with only ten cases reported worldwide.

We present a case of a 73-year-old male with a history of esophageal adenocarcinoma treated with neoadjuvant chemoradiation therapy and esophagectomy. Nine months into adjuvant Nivolumab, he developed lower urinary tract symptoms and bilateral hydronephrosis. Cystoscopy revealed diffuse erythematous bladder mucosa without papillary lesions. Biopsies obtained during transurethral resection of the bladder tumor (TURBT) demonstrated invasive adenocarcinoma of the bladder, consistent with metastatic esophageal adenocarcinoma. An additional explorative laparoscopy showed peritoneal nodules consistent with metastatic spread. Systemic therapy was changed from Nivolumab to FOLFOX. After eight cycles of FOLFOX, the patient ultimately developed disease progression with lung metastases and expired six months after TURBT.

To the best of our knowledge, this is the first reported case of esophageal adenocarcinoma metastasizing to the urinary bladder during adjuvant immunotherapy.

Key words: adenocarcinoma; bladder; esophageal cancer; metastatic; nivolumab

Abbreviations

CT – Computed Tomography

TURBT – Transurethral Resection of Bladder Tumor

IHC – Immunohistochemistry

LUTS – Lower Urinary Tract Symptoms

FOLFOX – Folinic Acid, Fluorouracil, Oxaliplatin

Introduction

Esophageal cancer is the seventh most common malignancy worldwide [1]. Despite advances in diagnosis and multimodal therapy, long-term survival outcomes remain poor. The overall 5-year survival rate is 48.7% for patients with localized disease, decreases to around 28.4% in those with regional lymph node involvement, and drops to 5.4% in the presence of distant metastases [2].

Metastatic spread of esophageal cancer can occur via direct invasion, lymphatic spread, or hematogenous routes [4]. The most frequent sites of metastasis include regional lymph nodes, liver, lungs, bone, and adrenal glands. Distant metastasis of esophageal cancer to the bladder is extremely uncommon, with only ten cases reported in the literature to date [4-13]. All previously reported cases were associated with poor prognosis.

We present a rare case of esophageal adenocarcinoma metastasizing to the urinary bladder during adjuvant immunotherapy with Nivolumab.

Case presentation

The patient is a 73-year-old male with a history of esophageal adenocarcinoma of the lower third of the esophagus. There was no evidence of metastatic disease on imaging at the time of diagnosis. Patient was treated with neoadjuvant chemotherapy (five cycles of carboplatin and paclitaxel) and radiation therapy (23 fractions of 41.4 Gy), followed by minimally invasive esophagectomy 3 months after diagnosis [14]. Final pathological staging was ypT2N1aR0, representing tumor growth into the muscularis propria and involvement of a single peri-esophageal lymph node. Given nodal positivity and a positive PD-L1 expression of

the resected specimen (Combined Positive Score (CPS) of 15), the patient was planned to be treated with adjuvant immunotherapy Nivolumab for 12 months [15]. Follow-up CT imaging (thorax/abdomen) after 3 and 6 months postoperatively showed no evidence of disease recurrence or metastasis.

Eleven months postoperatively and nine months after the start of Nivolumab, the patient presented with lower urinary tract symptoms (LUTS) (urgency, nocturia, and suprapubic pain). Imaging revealed bilateral hydro-ureteronephrosis with diffuse bladder wall thickening. Urine cultures were negative, and renal function remained stable, with a serum creatinine of 1.25 mg/dL.

The patient underwent an elective diagnostic cystoscopy and TURBT. The diagnostic cystoscopy (see Figure 1) showed diffuse erythematous and edematous bladder mucosa without any distinct papillary or nodular suspicious lesions. Random cold biopsies and targeted warm biopsies of the erythematous regions were obtained. Retrograde ureteroscopy was not possible; therefore, a retrograde ureterography (see Figure 2) was performed, which showed bilateral distal ureteral stenosis approximately 3 cm proximal to the ureteric orifices, raising suspicion of external compression.

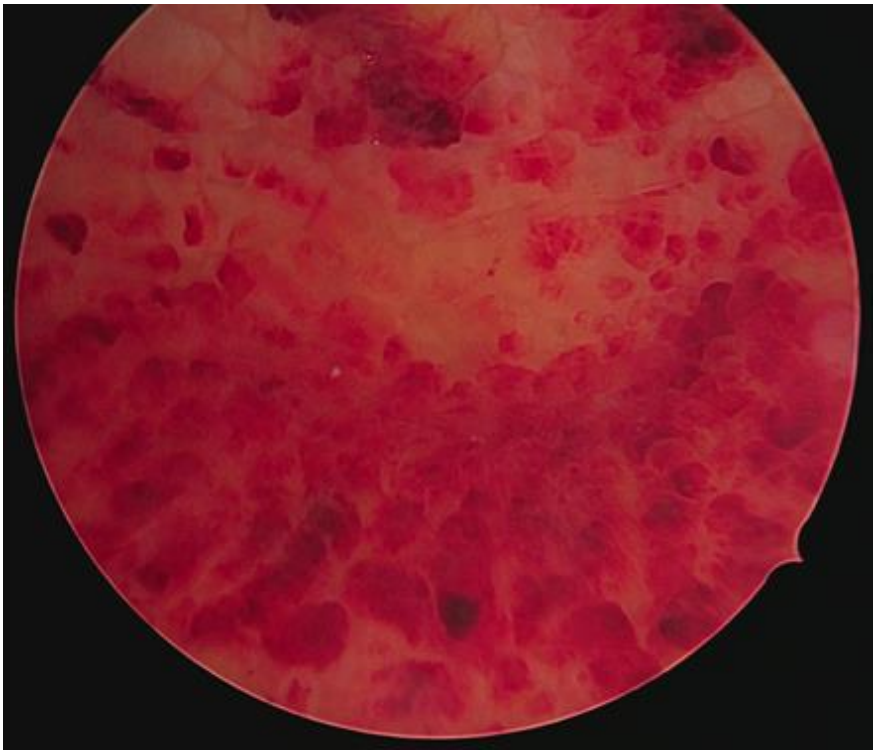

Figure 1: Diagnostic cystoscopy with erythematous and edematous bladder mucosa

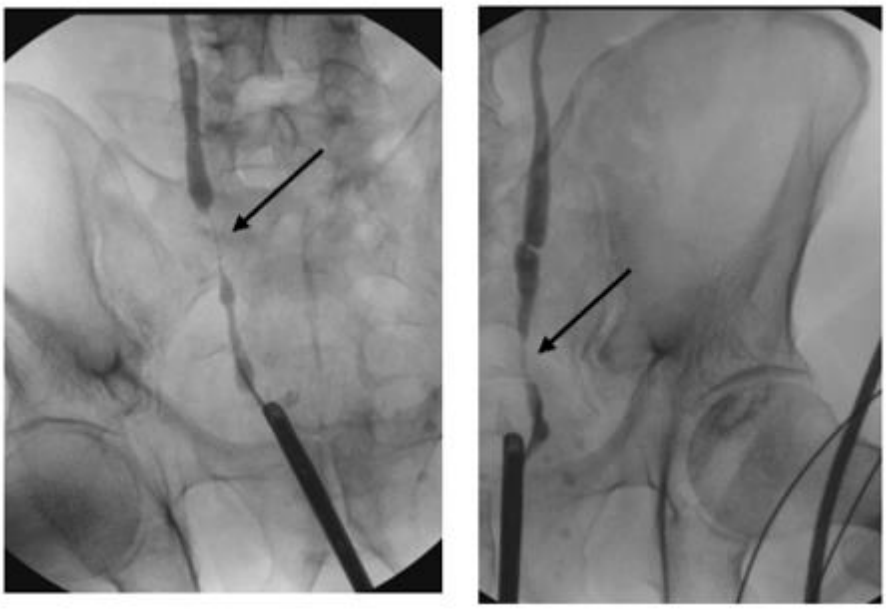

Figure 2: Retrograde ureterography showing bilateral distal ureteral stenosis

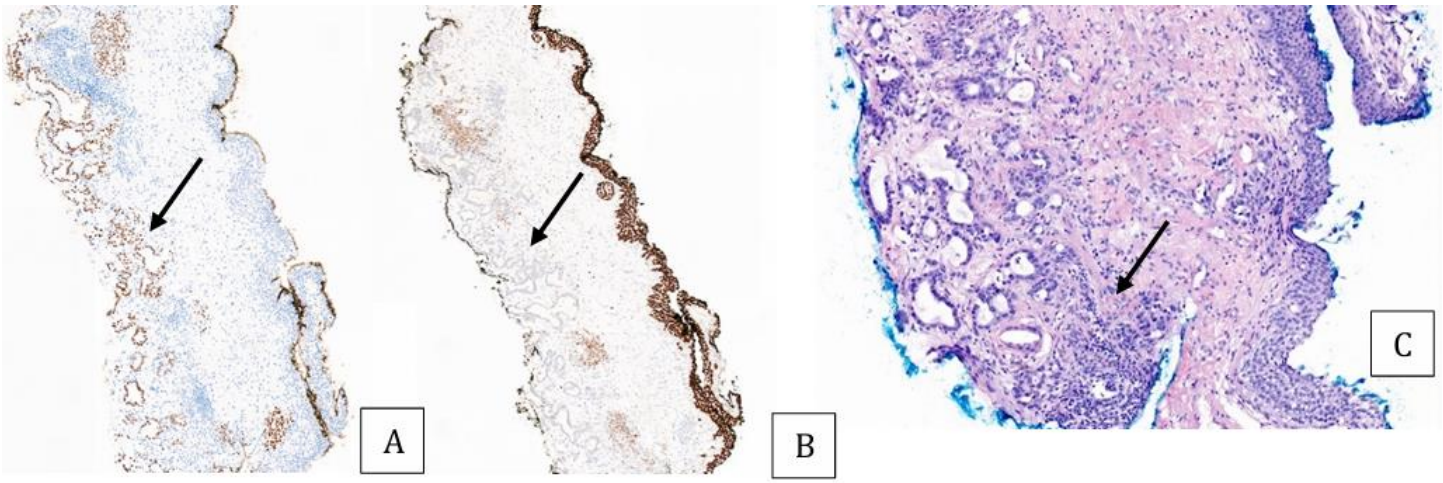

Figure 3: Immunohistochemical staining of the bladder tumor (a. Positive stain for CDX-2, b. Negative stain for GATA3, c. Hematoxylin and eosin (H&E) image of esophageal adenocarcinoma involving the urinary bladder).

Pathology from the TURBT (cold and warm) revealed invasive adenocarcinoma comparable to the patient's known esophageal adenocarcinoma. Immunohistochemical staining was positive for p53 and Caudal Type Homeobox 2 (CDX2), and negative for GATA3 and Cytokeratin 20 (CK20), confirming metastatic esophageal adenocarcinoma (see Figure 3).

Subsequent PET-CT scan showed diffuse hypermetabolic and infiltrative changes in the transverse colon, peritoneal fat, and bladder. Serum carcinoembryonic antigen (CEA) analysis was elevated at 11.5 μg/L, consistent with systemic tumor activity.

Given these findings, an explorative laparoscopy was performed, revealing a dense inflammatory reaction surrounding the urinary bladder and nodular peritoneal changes in both left and right fossae (see Figure 4), from which biopsies were obtained. Concomitantly, bilateral ureteral stents were placed prophylactically to prevent postrenal kidney failure. Stent placement had not been performed earlier, as the patient was asymptomatic and renal function remained stable. Pathology and immunohistochemical staining confirmed the presence of peritoneal disease.

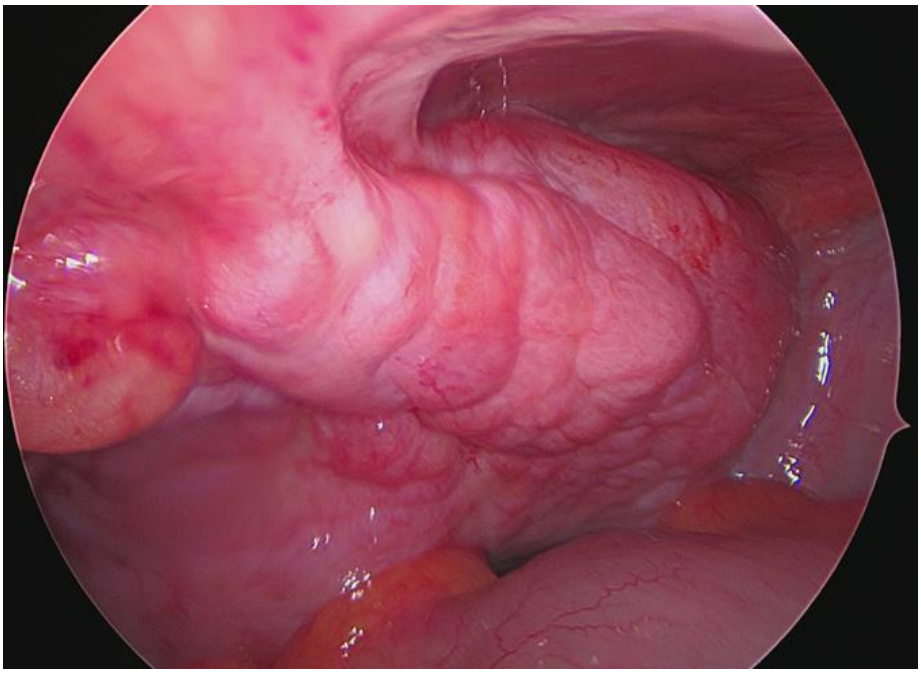

Figure 4: Explorative laparoscopy with an inflammatory reaction around the bladder

The patient was switched from immunotherapy (Nivolumab) to chemotherapy (FOLFOX) [16]. After four cycles of FOLFOX, follow-up CT imaging (thorax/abdomen) revealed radiographic progression with multiple bilateral lung metastases. Multidisciplinary consultation advised continuing with FOLFOX, as the CEA level dropped significantly to 5 μg/L. The patient ultimately expired approximately 6 months after his TURBT and following eight cycles of FOLFOX chemotherapy.

Discussion

Metastatic esophageal adenocarcinoma spreading to the bladder is a rare phenomenon.

In most cases, bladder involvement is the result of direct extension from nearby pelvic organs (colon, prostate, rectum, or cervix) [17].

Distant metastases can occur through three principal pathways: lymphatic, venous, or arterial [3]. The most common sites of distant metastasis for esophageal adenocarcinoma are the liver and the lungs through the portal venous system and the vena cava, respectively. The mechanism to other distal organs is still unknown. Shaheen et al. suggest an arterial spread where an esophageal tumor embolus enters the arterial circulation and travels through major arteries to seed a distal terminal organ [3].

An extensive literature search found only 10 reported cases of metastatic disease to the urinary bladder originating from esophageal cancer [4-13]. These cases are summarized in Table 1. The patients were predominantly male (70%), and the majority of metastases occurred metachronously, developing months after detection of the primary tumour. Survival outcomes were highly variable, ranging from a few weeks to several months following TURBT, with some patients remaining alive at last follow-up.

Author	Publication year	Age (year)	Sex	Survival/death (months)	Timing metastasis	cStage (first visit)	IHC status of bladder	IHC status of esophagus
Hargunani et al. [4]	2005	68	Female	4 months after TURBT	Metachronous	NS	NS	NS
Schuurman et al. [5]	2009	53	Male	NS	Synchronous	T3N0M1 stage IVb	CK7+, CK20 +, CDX2+	CK7+, CK20 + and CDX2+
Katz et al. [6]	2017	49	Female	3 weeks after TURBT	Metachronous	T3N4M1 Stage IVb	CK7+, CK20 +, CDX2+, GATA3 -, Uroplakin -	HER2+
Goh et al. [7]	2019	72	Male	Survival	Metachronous	pT4aN0M0	CK7+, CK20+, CDX2 -, GATA3-	NS
Ramakrishnan et al. [8]	2020	50s	Male	Survival	Metachronous	ypT3N1M0	CK7+, CDX2+, GATA3 -, p63-, NKX3.1-	HER2+
Toyota et al. [9]	2020	75	Male	Survival	Metachronous	T1bN0M0 stage I	CK7+, CK20−, CDX2+, MUC5AC+, p53+	CK7+, CK20−, CDX2+, MUC5AC+, p53+
Wignall et al. [10]	2021	71	Male	NS	Synchronous	NS	CDX2+, CK20+, CAM5.2+, GATA3-	CDX2+, CK20+, CAM5.2+, GATA3-
Liu et al. [11]	2022	68	Female	9 months after TURBT	Metachronous	ypT3N1M0	CK7+, CDX2+, CK20 -, GATA3 -	CK7+, CDX2+, CK20 -, GATA3 -
Olawoyin et al. [12]	2023	83	Male	Survival	Metachronous	T3N3M0	CDX2+, CAM5.2+, GATA3 +, CK7-, CK20-, NKX3.1-	NS
Zhang et al. [13]	2025	57	Male	Survival	Metachronous	T2N1M0 (SCC)	CK5/6+, GATA3+, CK7-, CK20-, Uroplakin II-	CKP+, CD34-, D2-40-
Our case	**2025**	**73**	**Male**	**6 months after TURBT**	**Metachronous**	**ypT2N1aR0M0**	**CDX2+, p53+, GATA3-, CK20-**	**NS**

Table 1: Case reports of esophageal cancer with bladder metastasis

Abbreviations: Caudal Type Homeobox 2 (CDX2), Cluster of Differentiation 34 (CD34), Cytokeratin 5/6 (CK 5/6), cytokeratin 7 (CK7), cytokeratin 20 (CK20), Cytokeratin Pan (CKP), Human Epidermal Growth Factor Receptor 2 (HER2), immunohistochemistry (IHC), Mucin 5AC (MUC5AC), NK3 Homeobox 1 (NKX3.1), not specified (NS), Podoplanin (D2-40 antibody), squamous cell carcinoma (SCC), and transurethral resection of the bladder (TURBT)

In these rare cases, immunochemistry played a pivotal role in establishing the diagnosis. Immunohistochemical profiling typically demonstrated positivity for CDX2, consistent with gastrointestinal origin, and negativity for GATA3, which is characteristically expressed in urothelial carcinoma [10]. In contrast, expression of CK7 and CK20 was variable and therefore less specific for determining the site of origin.

Conclusion

Metastasis to the bladder from esophageal adenocarcinoma is extremely rare. Our case was the first to show involvement of the bladder during immunotherapy. Nevertheless, prognosis remains extremely poor. In patients presenting with atypical LUTS and a history of an aggressive solid organ malignancy, despite previous curative treatment, metastatic disease should remain an important differential diagnosis.

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Conflict of Interest

The authors declare no conflict of interest.

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