



## Oncology

## Exceptional response to immunotherapy in association with radiotherapy in patient with breast metastasis from urothelial carcinoma: A case report

Giulia Bonfante<sup>a,\*</sup>, Emanuela Fantinel<sup>b</sup>, Cristina Masini<sup>b</sup>, Franco Bergamaschi<sup>c</sup>, Salvatore Micali<sup>a</sup>, Bernardo Rocco<sup>a</sup>

<sup>a</sup> Department of Urology, University of Modena and Reggio Emilia, 41124 Modena, Italy

<sup>b</sup> Department of Medical Oncology, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy

<sup>c</sup> Department of Urology, Azienda USL-IRCCS di Reggio Emilia, 42123 Reggio Emilia, Italy



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## ABSTRACT

Most common sites of metastasis of urothelial carcinoma (UC) are lungs, liver, lymph nodes and bone. Pembrolizumab, a humanized monoclonal antibody directed against programmed cell death protein-1 (PD-1), represents an effective second-line therapy for advanced UC. Radiotherapy has been shown to induce a mechanism of immunogenic cell death (ICD) resulting in immune memory and advantageous systemic effects. We present the first case of breast metastasis (BM) from a UC described in literature who had an exceptional response to second-line therapy with pembrolizumab in association with radiotherapy, showing the efficacy of combining immunotherapy and radiotherapy even in patients with atypical metastatic sites.

## Introduction

UC is one of the most widespread cancers worldwide, with around 430,000 new diagnoses each year. Most patients have a superficial non-muscle invasive disease, whereas about 30%–40% presents at diagnosis or develops muscle-invasive and/or metastatic disease, and atypical sites of metastasis are rare.<sup>1</sup>

Although platinum-based chemotherapy remains the standard first-line treatment for patients with metastatic UC rarely achieve complete and durable response, with a 5-year overall survival (OS) rate of 15% and after failure, there were few data available for the choice of second-line treatment.<sup>2</sup>

New knowledge about mechanism of UC progression and involvement of immune system led to development of immune checkpoint inhibitors (ICIs) targeting either PD-1 or PD-L1 that have shown efficacy in different settings of UC. In phase III trial KEYNOTE-045, pembrolizumab improved OS compared with control arm in patients with metastatic UC progressed during or after platinum-based chemotherapy, regardless of PD-L1 tumour expression status and with good tolerability.<sup>3</sup>

## Case presentation

In this reported case, a 61-year-old woman presented to emergency room due to new-onset macrohematuria and irritative voiding symptoms. An abdomen ultrasound (US) showed a vascularized mass (Ø 70 × 70 mm) in basal right-side wall of bladder and initial right hydronephrosis. The patient was hospitalized and received blood transfusions for anaemia caused by haematuria (Hb 4.8 gr/dl). Blood tests also reported an increase in creatinine basal level from 1.37 to 1.8 mg/dl.

Abdomen and chest CT scan confirmed the presence of intraluminal mass (Ø 70 × 60 mm) involving right half of the bladder and showed a lymphadenopathy (Ø 31 × 26 mm) in right iliac region. Other lymph nodes appeared bilateral along external iliac vessels, the largest on left side (maximum short axis 13 mm). There was no evidence of metastatic disease at baseline CT scan and bone scintigraphy.

Pathological investigation of specimens obtained by transurethral resection of bladder tumour (TURBT) showed a high-grade urothelial papillary carcinoma with invasion of lamina propria (pT1 WHO 2016). The absence of detrusor muscle in the sample probably underestimated the disease. To have an accurate staging and to stop bleeding, a salvage radical cystectomy with an extended lymphadenectomy and an ureterocutaneostomy was performed. Post-surgical staging was pT3b N1 M0

\* Corresponding author. Policlinico di Modena, Dept. Of Urology, Via del Pozzo, 71, Modena, 41124, Italy.

E-mail addresses: [giuliabonfante89@gmail.com](mailto:giuliabonfante89@gmail.com) (G. Bonfante), [manuf86@hotmail.it](mailto:manuf86@hotmail.it) (E. Fantinel), [cristina.masini@ausl.re.it](mailto:cristina.masini@ausl.re.it) (C. Masini), [francoantonimario.bergamaschi@ausl.re.it](mailto:francoantonimario.bergamaschi@ausl.re.it) (F. Bergamaschi), [salvatore.micali@unimore.it](mailto:salvatore.micali@unimore.it) (S. Micali), [bernardo.rocco@gmail.com](mailto:bernardo.rocco@gmail.com) (B. Rocco).

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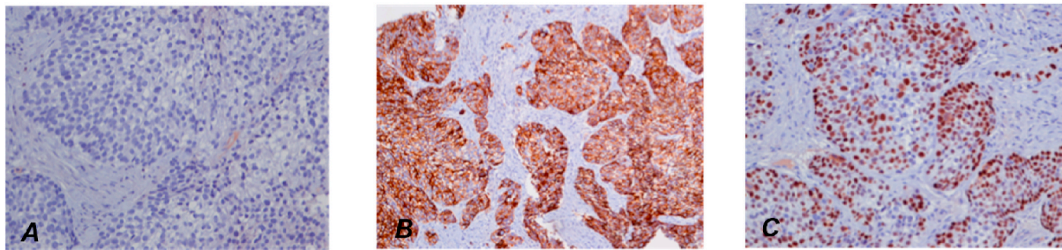
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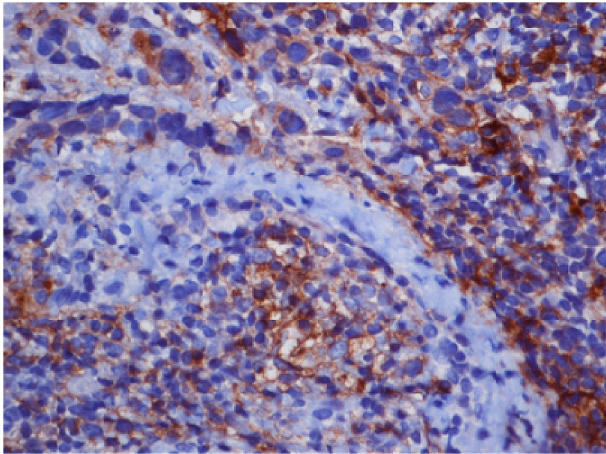
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**Fig. 1.** Immunohistochemistry of breast metastasis. **A)** negative value for estrogenic receptor (ER); **B)** positive value in brown for CK20; **C)** positive value in brown for p63. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 2.** Immunohistochemistry of breast metastasis. *PD-L1* CPS 30%: tumour cells and infiltrating immune cells expressing PD-L1 in brown. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(sec WHO 2016).

During post-operative hospitalization, patient found a right breast nodule through breast self-examination, confirmed by mammography

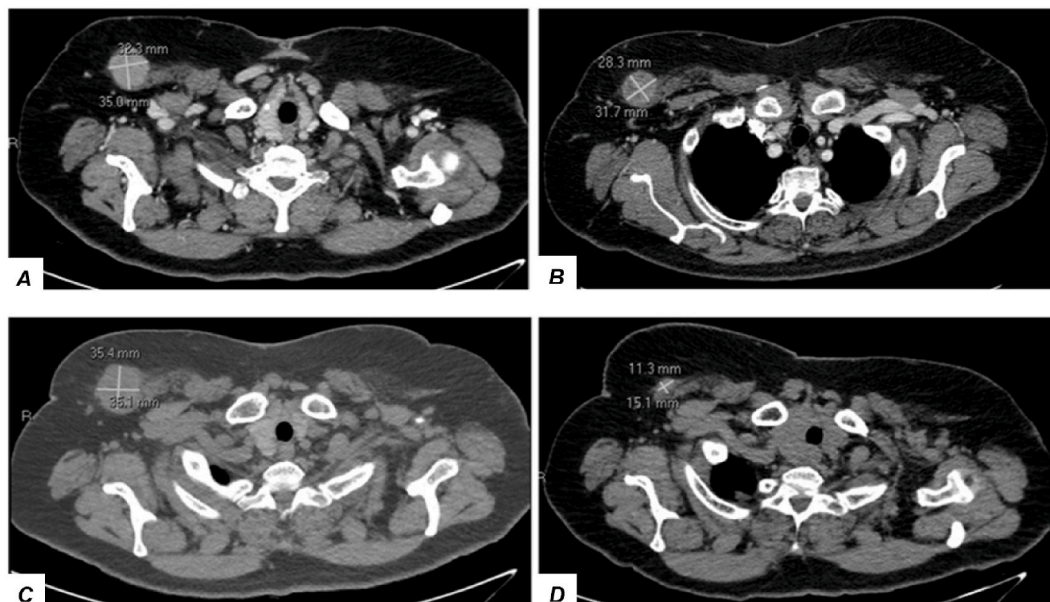
and US ( $\varnothing$  25 × 35 mm). The histological and immunohistochemistry (estrogenic receptor negative, CK20 positive, p63 positive) examination of needle biopsy was diagnostic for a metastatic localization from UC (Fig. 1).

The CT scan performed after surgery revealed the presence of a subcutaneous nodule on the left side of thorax wall ( $\varnothing$  13 × 18 mm) and a lymphadenopathy (short axis <15 mm) near external left iliac artery.

Given the evidence of metastatic disease, patient underwent a first-line chemotherapy regimen with carboplatin and gemcitabine. After 3 cycles radiological assessment showed a partial response of breast metastasis (reduced to  $\varnothing$  32 × 28 mm) according to RECIST v 1.1 criteria. After 6 cycles of chemotherapy, imaging showed disease progression. Target breast lesion increased to  $\varnothing$  35 × 35 mm and CT scan revealed numerical and dimensional increase of lymph nodes in para-aortic region.

We performed a genomic analysis supported by FoundationOne®CDx on tissue samples obtained by breast biopsy, which identified alterations in genes *BCL2L1*, *CDKN2A*, *MYC*, *RAF1*, *TP53* known to be cancer related. No actionable mutations were identified. Immunohistochemical test of PD-L1 was then performed with IHC 22C3 antibody (Dako North America) and evaluated with Combined Positive Score (CPS = percentage of PD-L1 expressing tumour and infiltrating immune cells relative to total number of tumour cells).<sup>3</sup> PD-L1 expression was 30% (Fig. 2).

Considering disease progression and results of genetic and immunohistochemical analyses, patient underwent a second-line treatment



**Fig. 3.** Computed Tomography (CT) Images of the breast metastasis. **A)** CT scan after cystectomy (January 2019); **B)** partial response at CT scan after three cycles of chemotherapy (April 2019); **C)** disease progression at CT scan after six cycles of chemotherapy (July 2019); **D)** response after radiotherapy and pembrolizumab (October 2019).

with pembrolizumab at dose of 200 mg every three weeks. A concurrent stereotactic radiotherapy treatment (6X FFF photon beams with a total dose of 30 Gy in 3 fractions) was performed on breast and subcutaneous metastasis of chest wall.

After stereotactic radiotherapy and 4 cycles of pembrolizumab, radiological assessment showed a complete response of subcutaneous metastasis of chest wall and a significant reduction of right breast nodule (lesion size reduced to  $\varnothing 15 \times 11$  mm). Abdomen lymph nodes were also reduced, with non-pathological residual dimensions (short axis <10 mm) (Fig. 3).

## Discussion

Before immunotherapy, median OS for patients with advanced UC was 9 months and no established therapy was available after failure of platinum-based treatment. Development of ICIs has improved both OS and quality of life of patients in a second-line therapy setting, with a better safety profile compared to traditional chemotherapy.<sup>3</sup> In our patient pembrolizumab was well tolerated, reporting only low-grade hyperthyroidism (grade 2 sec. CTCAE v 5.0) treated and resolved with medical therapy.

The biological rationale for therapeutic efficacy of pembrolizumab was suggested by molecular characterization of breast metastatic tissue, which resulted in PD-L1 CPS of 30%. Although in KEYNOTE-045 trial survival benefit was observed in the total population regardless of PD-L1 CPS expression, in subgroup analysis the benefit was better in patients with PD-L1 CPS of 10% or more.<sup>3</sup>

In our clinical case, the exceptional response of metastasis treated with radiotherapy could be related to an ICD mechanism that supported the action of the immunotherapy. In fact, it is well known that radiotherapy has direct cytotoxic effects on tumour cells (targeted effects) primarily due to production of DNA double-strand breaks. More recent

evidence has shown that radiotherapy induces phagocytosis of tumour cells by dendritic cells (DC) and processing of tumour-derived antigens and DC-associated cross-priming of CD8+CTLs.<sup>4</sup> Therefore, ICD may involve the recruitment of host's immune system, resulting in immune memory and advantageous systemic effects, such as the abscopal effect, which causes tumour regression in non-irradiated areas.<sup>5</sup>

## Conclusions

This reported case of atypical BM of UC confirms that immunotherapy represents an excellent therapeutic choice for patients with metastatic UC progressed after platinum-based chemotherapy. The association of immunotherapy with radiotherapy could have a synergistic effect on changes of tumour microenvironment and it could increase disease control.

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