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UNFORESEEN COMPLICATIONS OF PEMBROLIZUMAB IN BREAST RECONSTRUCTION POST-MASTECTOMY

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ABSTRACT

A 53-year-old post-menopausal Indian female presented with invasive ductal carcinoma, treated with neoadjuvant chemotherapy and pembrolizumab due to a PD-L1 combined positive score of 5. Following a right mastectomy and axillary dissection, she received a breast expander and AlloDerm™ graft. After resuming pembrolizumab and paclitaxel postoperatively, she developed severe breast redness and high-grade fever, necessitating expander removal due to suspected pembrolizumab-induced complications. This case underscores the unique and severe adverse effects of pembrolizumab on breast reconstruction, highlighting the need for careful monitoring and management in patients undergoing similar treatments.

KEYWORDS

Pembrolizumab, breast reconstruction, breast cancer

LEARNING POINTS

- Among patients with early triple-negative breast cancer, the combination of pembrolizumab with neoadjuvant chemotherapy enhances outcomes compared to chemotherapy alone.
- Early recognition is essential for managing pembrolizumab-induced complications, as demonstrated by the need for expander removal and debridement in this case.
- The unique adverse effects observed in this case underscore the importance of tailoring cancer treatment plans to individual patients, taking into account the potential risks associated with immunotherapy in the context of reconstructive surgery.

INTRODUCTION

Breast cancer treatment often requires a multidisciplinary approach, with surgical interventions such as mastectomy followed by breast reconstruction being pivotal for patient recovery and quality of life. Pembrolizumab – an anti-PD-1 therapy – has demonstrated efficacy across various cancers, including breast cancer. However, its potential adverse effects on the breast reconstruction process remain insufficiently explored. Here, we present a case highlighting the unforeseen complication of pembrolizumab on breast tissue expander dissolution post-mastectomy and discuss its implications for patient care.

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CASE DESCRIPTION

We describe the case of a 53-year-old post-menopausal Indian female with a past medical history of obesity, dyslipidaemia and asthma, who had abnormal findings on a screening mammogram in December 2021. Magnetic resonance imaging showed a 4.6 cm mass in the right breast with several satellite lesions, and no suspicious masses in the left breast. A biopsy was performed, which showed evidence of invasive ductal carcinoma. The patient had a Nottingham score of 9/9, triple-negative (weak oestrogen receptor (ER) positivity of 5%), and a Ki-67 of 70%. Genetic testing revealed *RAD51C* positivity. Treatment ensued with neoadjuvant therapy consisting of doxorubicin and cyclophosphamide for total of four cycles; pembrolizumab was added to the regimen after testing for PDL1 showed a combined positive score of 5. The patient experienced some adverse effects such as fatigue and pruritus, which later resolved.

In May 2022 she underwent a right mastectomy with sentinel lymph node biopsy that was positive and completed a full axillary dissection. Pathology showed evidence of a residual invasive ductal carcinoma measuring 1.5 cm with negative surgical margins, and one of thirteen axillary nodes positive for residual invasive carcinoma. A right breast expander and AlloDerm™ graft were placed immediately, without complications. Four weeks postoperatively, we resumed pembrolizumab with adjuvant paclitaxel.

In July 2022 at her first follow-up appointment, the patient reported experiencing mild breast redness and a low-grade fever the day after receiving pembrolizumab. These symptoms resolved spontaneously, and her treatment regimen was continued without changes. However, following her second exposure to pembrolizumab, she developed significant breast redness and a high-grade fever the next day. Examination of the right breast revealed notable redness and tenderness on palpation, though no boggy areas were palpable *(Fig. 1)*. A complete blood count and comprehensive metabolic panel showed no overt abnormalities. Despite being prescribed antibiotics, the symptoms persisted.

Consequently, the patient was referred to plastic surgery for further evaluation. She underwent debridement, expander removal and the placement of drains. Intraoperatively, turbid fluid and a biofilm were observed coating the pocket where the expander had been placed. Due to the temporal association of both mild and severe reactions with pembrolizumab administration, the drug was indefinitely discontinued. The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 5, indicating that the adverse reaction was probably due to the immunotherapy rather than a simple case of mastitis.

In the third week of August, the patient's drains were removed, and she was restarted on paclitaxel therapy. Pembrolizumab was permanently discontinued. She subsequently completed single-agent paclitaxel in the adjuvant setting without experiencing any side effects. Following this, she underwent radiation therapy over 33 fractions without undue effects. She is currently awaiting the placement of a right breast implant, having completed all adjuvant therapy and remaining in good health *(Fig. 2)*.

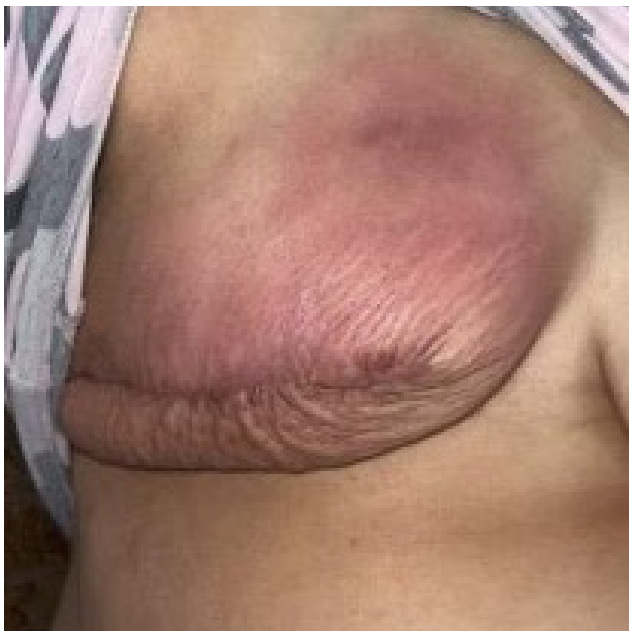

Figure 1. Inflammation of the breast due to underlying breast tissue expander rejection.

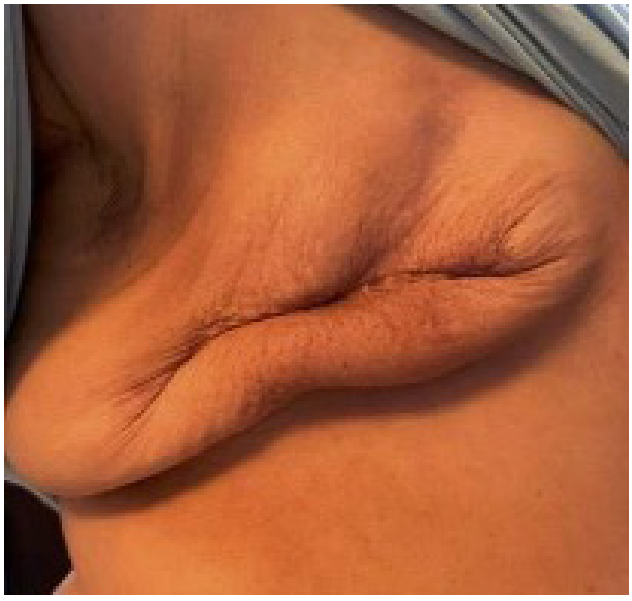

Figure 2. Image of the right breast post removal of tissue expander and debridement.

DISCUSSION

Pembrolizumab is a humanised monoclonal antibody that targets the programmed death (PD-1) receptor protein and has been developed to treat a multitude of malignancies. The drug was the first anti-PD-1 therapy approved in the United States by US Food and Drug Administration. It was initially approved to treat advanced, unresectable or metastatic malignant melanoma cases that failed therapy with ipilimumab, and those with BRAF V600 mutation in the United States; however, the spectrum of cancers it has been approved for has expanded since[1].

Results of a randomised phase III trial involving 1,174

patients with untreated, early triple-negative breast cancer concluded that patients in the 'pembrolizumab with chemotherapy' cohort had a higher percentage of pathological complete response at the time of surgery than patients in the 'placebo with chemotherapy' cohort[2]. Our patient had ER 5%, PR 0%, HER2 negative breast cancer, classifying it as a triple-negative breast cancer despite the ER being 5%. She received weekly paclitaxel, a chemotherapeutic drug, with pembrolizumab post right mastectomy and placement of a tissue expander and AlloDerm™.

Immune-related adverse effects such as rash, colitis, hepatitis, pneumonitis and endocrinopathies mark pembrolizumab use. The primary treatment for such effects involves immunosuppressants such as corticosteroids and infliximab[3]. Some uncommon cases of adverse effects associated with the administration of pembrolizumab, as described in the literature, include acute tubulointerstitial nephritis, arthritis, type-1 diabetes mellitus, encephalopathy, haemophagocytic histiocytosis, hepatotoxicity, non-ST-elevation myocardial infarction, necrotic myositis and scleroderma, in addition to autoimmune haemolytic anaemia and pancytopenia[4,5]. According to literature on the adverse effects of pembrolizumab, our case is the first where pembrolizumab resulted in the destruction of a breast tissue expander.

Cases of pembrolizumab-associated rejection documented in the literature include corneal rejection, coronary allograft rejection, kidney transplant rejection and liver transplant rejection[6,7]. Anti-PD-1 therapies have the highest risk of graft rejection in transplant patients (40%) and account for nearly three-quarters of total graft rejections, whereas one-fifth of rejections occur due to a combination of PD-1/CTLA-4[8]. In our patient's case, AlloDerm™ was the allograft that was impacted by initiating pembrolizumab. The median onset time from pembrolizumab initiation to graft rejection is 23 (1–77) days[7]. For our patient, this duration was 45 days. According to a study of 1,037 patients who underwent the placement of a tissue expander, the rate of total post-operative complications was 31.8%. A complication was categorised as a major complication if it necessitated surgical intervention. Radiation nearly doubled the rate of major complications, from 21.2% to 45.4%. Despite a higher rate of major complications, nearly 70% of the patients who received radiotherapy had successful breast reconstruction using implants[9]. We believe there is a direct correlation with the effects of immunotherapy that led to our patient's presentation of breast tissue expander dissolution, necessitating removal of the expander and debridement of the breast tissue. Our patient did not receive radiotherapy until after removing a tissue expander, thereby ruling radiotherapy out as a possible cause of the tissue expander dissolution.

CONCLUSION

Mastectomy with tissue expander placement and AlloDerm™ are commonly used for patients seeking reconstruction following mastectomy, for a breast cancer diagnosis. Our case highlights the potential for pembrolizumab, an anti-PD-1 therapy, to cause severe adverse reactions that complicate the breast reconstruction process post-mastectomy. Clinicians must have a high degree of suspicion for such potential complications associated with immunotherapeutic drugs. This heightened awareness can lead to an early diagnosis, aiding in appropriate treatment strategy planning and implementation, preventing further complications and undue adverse effects on our patient population.

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