Title

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Authors

Kathuria-Prakash, MD, Nikhita
Callahan, Rena D.

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CLINICAL VIGNETTE

Renal Failure from Pembrolizumab: A Lesser-Known Toxicity of Immunotherapy

Nikhita Kathuria-Prakash, MD and Rena D. Callahan, MD

Introduction

Pembrolizumab is an anti-programmed death-1 (PD-1) protein monoclonal antibody. It is one of the commonly used immune checkpoint inhibitor (ICI) antineoplastic agents. Pembrolizumab was first approved by the US Food & Drug Administration in 2014 for advanced melanoma, and now carries multiple indications in the adjuvant and metastatic settings across a variety of malignancies. Immune checkpoint inhibitors have a different adverse event profile when compared with cytotoxic chemotherapy and are often very well tolerated. Pembrolizumab blocks inhibition of the body's immune response to cancer. However, in doing so, it can stimulate autoimmunity. As pembrolizumab is increasingly used, many immune-related adverse events (irAEs) are being observed. There is a wide spectrum of irAEs, ranging from the commonly encountered mild rash, thyroiditis, and elevated liver enzymes to the less frequent and more serious adverse events, including myocarditis, hypophysitis, fulminant hepatitis, and renal failure. We describe a woman who received neoadjuvant pembrolizumab with chemotherapy for inflammatory breast cancer and developed renal failure attributable to pembrolizumab.

Case Description

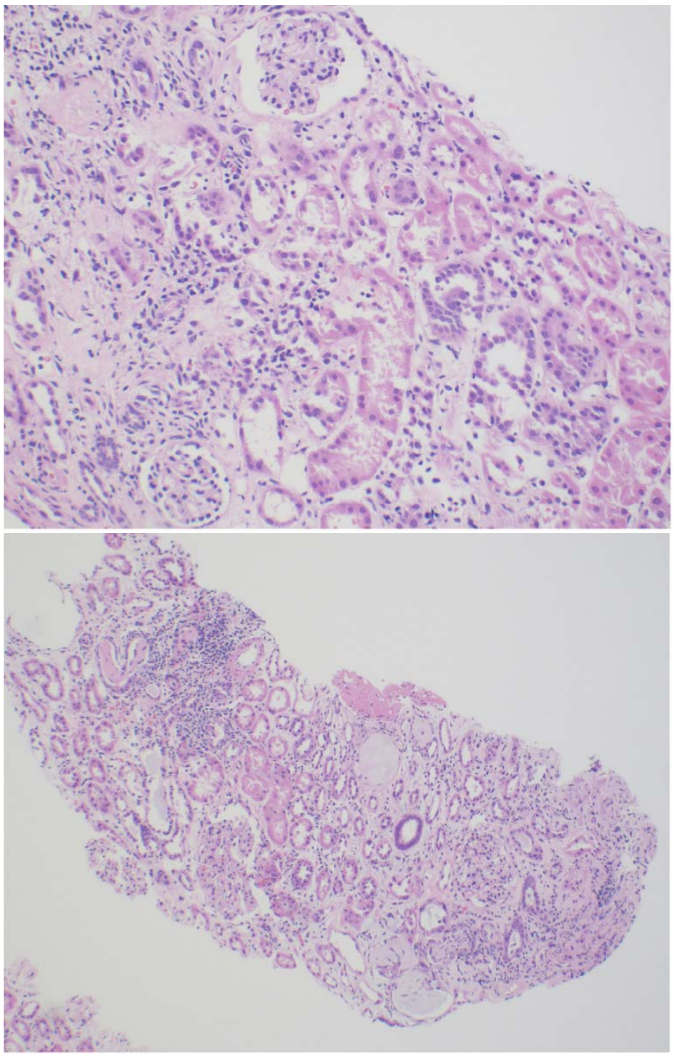
A 54-year-old female with a past medical history of GERD, hypothyroidism, and vitamin D deficiency presented to her primary care physician with right breast tenderness and swelling. Her screening mammogram two months prior was normal, showing only heterogeneously dense breasts and benign appearing calcifications. Her physician noted induration and erythema in her right breast, with axillary adenopathy on physical exam. Repeat mammogram showed increased density throughout the breast, moderate diffuse skin thickening, and six morphologically abnormal lymph nodes. MRI showed diffuse non-mass enhancement occupying the almost entire right breast, extending to the subareolar skin, suspicious fat stranding between the enhancement and the underlying pectoralis major, and right axillary and internal mammary lymphadenopathy. Pathology obtained from core needle biopsy showed grade 3 invasive mammary carcinoma with extensive lymphovascular invasion. Axillary lymph node biopsy also showed invasive carcinoma. Biomarkers, including estrogen receptor, progesterone receptor, and HER2, were negative. She was diagnosed with poorly differentiated, high grade, triple-negative inflammatory breast carcinoma. She had a clinical T4N3 tumor and was referred to oncology for neoadjuvant systemic treatment. Due to her aggressive malignancy, she was initiated on immunotherapy and chemotherapy with pembrolizumab, carboplatin, and docetaxel. The patient was aware of the off-label use of pembrolizumab, but wanted to proceed due to Phase III data showing increased rates of pathologic complete response with this agent.

Her neoadjuvant therapy course was complicated by a rash and ankle edema. The rash was evaluated by dermatology and diagnosed as fungal intertrigo in the setting of immunosuppression. The ankle edema was thought to be an adverse effect of the docetaxel and improved with furosemide. Her serum creatinine on day one of cycle one was 0.60 mg/dL (GFR>89 mL/min/1.73m2), and was 0.69 mg/dL (GFR>89 mL/min/1.73m2) after six cycles. Interval imaging showed significant improvement and partial resolution of the cancer. She completed six cycles of pembrolizumab, carboplatin, and docetaxel.

She then was started on neoadjuvant therapy with pembrolizumab, doxorubicin, and cyclophosphamide. After her second cycle, routine labs showed increased creatinine of 2.81 mg/dL (GFR 18 mL/min/1.73m2) from 0.69 mg/dL (GFR >89 mL/min/1.73m2) three weeks prior. Sodium was 137 mmol/L, potassium 3.6 mmol/L, bicarbonate 23 mmol/L, and urea nitrogen 38 mg/dL. She reported feeling more fatigued after this cycle and noted decreased urine output. She was prescribed prednisone 60 mg daily and urgently referred to nephrology for evaluation of acute kidney injury (AKI). Furosemide was discontinued. Repeat creatinine three days later was 3.23 mg/dL (GFR 18 mL/min/1.73 m2) and urea nitrogen was 56 mg/dL. Urinalysis showed 69 RBCs/HPF, 14 WBCs/HPF, 0-2 hyaline casts, and no urine eosinophils. The AKI was thought to be immunotherapy-induced from pembrolizumab. She was continued on prednisone, pembrolizumab was held, and she was scheduled for kidney biopsy.

Pathology from the kidney biopsy showed acute interstitial nephritis (AIN) and mild interstitial fibrosis and tubular atrophy, thought to represent medication-related injury (Figures 1 & 2). The infiltrates were diffuse and consisted of mostly lymphocytes. Diffuse acute tubular injury was also noted. Prednisone was slowly tapered, and creatinine improved to 1.14 mg/dL (GFR 54 mL/min/1.73m2) after two months. She completed the remaining two cycles of doxorubicin and cyclophosphamide. She underwent mastectomy and was found to have pathologic complete response to neoadjuvant therapy,

including all lymph nodes negative for carcinoma. She was scheduled for post-mastectomy radiation therapy and continued tapering the prednisone.



Figures 1 & 2: High power and low power views of diffuse inflammation and tubular injury consistent with acute interstitial nephritis suggestive of medication-related injury.

Discussion

Our patient received neoadjuvant pembrolizumab for triple-negative breast cancer and developed acute renal failure after eight cycles of immunotherapy. Renal biopsy confirmed AIN caused by pembrolizumab. She had a pathologic complete response to preoperative treatment with chemotherapy and immunotherapy, and her renal function improved with steroids.

Triple-negative breast cancer is typically treated with chemotherapy, although recent studies support addition of immunotherapy.[1-3] A recent phase III clinical trial by Cortes et al showed pembrolizumab improves progression-free survival when administered in combination with chemotherapy for metastatic or locally recurrent unresectable triple-negative breast cancer, compared to chemotherapy alone.[1] Pembrolizumab is now a guideline-recommended agent for these patients.[2] Our patient was treated with neoadjuvant pembrolizumab and chemotherapy based on a recent phase III clinical trial by Schmid et al, which showed a significant increase in the proportion of patients achieving pathological complete response after receiving pembrolizumab plus neoadjuvant chemotherapy compared to those who received placebo plus neoadjuvant chemotherapy.[3] Patients in the pembrolizumab arm had more frequent serious adverse events, although the incidence of renal dysfunction was not specifically reported.[3] Despite this evidence, the FDA recently rejected the request for accelerated approval of pembrolizumab as a neoadjuvant agent for breast cancer, and requested survival data prior to approval, partly because of the toxicities associated with ICI.[4]

As ICIs become more widely used, providers should be aware of the many adverse events associated with these medications. The frequency of irAEs varies with medication and dose.[5] Fatigue, dermatologic, and endocrine irAEs are the most common.[6] Renal dysfunction was rarely noted in pembrolizumab trials, with no reporting of renal dysfunction in the Schmid et al clinical trial,[3] and only two patients with reported renal dysfunction in the stage III clinical trial of pembrolizumab for patients with advanced melanoma.[7] However, with widespread use of ICI, more pembrolizumab-related renal toxicities are being reported.[8]

When AKI is recognized, all nephrotoxic medications should be stopped, including ICI. AKI evaluation should include urinalysis, renal ultrasound or other renal imaging, and renal biopsy.[9] Urinalysis may show proteinuria, microscopic hematuria, or aseptic leukocyturia.[8] Renal imaging should be done to evaluate for hydronephrosis, which would suggest a post-renal etiology of AKI.[9] Renal toxicity from pembrolizumab manifests as AIN, as was seen in this case, whereas renal toxicity from chemotherapy typically manifests as acute tubular necrosis.[9] Pembrolizumab may also cause acute tubular injury, which was also seen in this case, and minimal change disease.[8] If ICI-induced renal injury is noted on biopsy, ICI should be permanently discontinued. Because such an important oncologic management decision rests on the proper diagnosis of ICI-induced toxicity, kidney biopsy should be pursued to confirm the diagnosis if there are no contraindications.[10]

High-dose corticosteroids are the mainstay of treatment of ICI-induced AIN, along with cessation of the offending agent. Some patients may require temporary hemodialysis for acute renal failure, which may progress to chronic renal failure requiring long-term hemodialysis.[8] Most patients will have recovery of renal function with steroids and stopping the ICI, as with our patient.[8]

Pembrolizumab is becoming a more common antineoplastic agent, and consequently, its adverse events are becoming more common as well. Renal failure is a relatively rare irAE but can have significant consequences if not quickly recognized and treated. Our patient developed renal failure after eight cycles of

pembrolizumab, highlighting that irAE can occur at any time. With prompt evaluation including biopsy, the diagnosis of pembrolizumab-induced AIN was established, pembrolizumab was stopped, corticosteroids were started, and she recovered renal function. She had complete pathologic response with pembrolizumab and chemotherapy. Pembrolizumab may have contributed to her excellent response, and as its indications broaden, irAEs will likely increase. Providers should be aware of the various irAEs, even those that are rare. High clinical suspicion and pursuing early confirmatory diagnostics are key to effective identification and management of irAEs.

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