

Autoimmune Granulomatous Inflammation of Lacrimal Glands and Axonal Neuritis Following Treatment With Ipilimumab and Radiation Therapy

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Summary: Immune checkpoint inhibitors such as anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), anti PD-1 (programmed cell death protein 1) and PD-L1 (programmed cell death protein-ligand 1) monoclonal antibodies are emerging as standard oncology treatments in various tumor types. The indications will expand as immunotherapies are being investigated in various tumors with promising results. Currently, there is inadequate identification of predictive biomarkers of response or toxicity. Unique response patterns include pseudoprogression and delayed response. The use of immune checkpoint inhibitors exhibit an unique toxicity profile, the immune-related adverse events (irAEs). The most notable immune reactions are noted in skin (rash), gastrointestinal track (colitis, hepatitis, pancreatitis), lung (pneumonitis), heart (myocarditis), and endocrine system (thyroiditis, hypophysitis). We present a patient with metastatic adenoid cystic carcinoma of the left submandibular gland with granulomatous inflammation of the lacrimal glands and axonal neuritis of the cervical and paraspinous nerves following treatment with ipilimumab and radiation therapy.

Key Words: granulomatous lacrimal glands inflammation, immune checkpoint inhibitors, axonal neuritis, ipilimumab

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CASE PRESENTATION

A 60-year-old man was diagnosed with adenoid cystic carcinoma of the left submandibular gland in April 2009 (T2N0M0).^{1–3} He underwent left submandibular gland resection and selective neck dissection followed by postoperative radiation therapy (total dose, 60 Gy in 30 fractions; completed, June 2009). He was monitored with imaging studies every 4–6 months. In August 2012, computed tomographic (CT) imaging revealed a well-circumscribed 1.2 cm nodule in the lingula. In May 2014, a lung biopsy confirmed metastatic adenoid cystic carcinoma; and next generation sequencing (409 genes) showed no alterations. In August 2014, CT imaging showed increase in the size and number of lung nodules and multiple peritoneal implants. In September 2014, the patient was referred to our phase I program for treatment. Molecular profile using the Foundation One platform showed a mutation in *TERT promoter-124C>T*. Immunohistochemical (IHC) analysis for PTEN showed retained expression and PD-L1 (clone 22C3; Dako) showed membranous staining in 0% of the tumor cells. In April

2015, the patient was enrolled on a clinical trial (NCT02009449) with pegylated interleukin (IL)-10.⁴ Overall, he tolerated the treatment well, although he experienced grade 3 thrombocytopenia requiring treatment delay and dose reduction. His disease was stable by RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. At the time of completion of 16 cycles (July 2016), his disease progressed and treatment was discontinued. In October 2016, he started treatment on a clinical trial (NCT02239900) with ipilimumab (anti-CTLA-4 antibody) (cytotoxic T-lymphocyte-associated protein 4) and stereotactic body radiation therapy (SBRT).⁵ His baseline imaging studies showed extensive metastatic disease to the lungs, lymph nodes, liver, peritoneum, and right ilium invading the psoas. Ipilimumab was to be administered at 3 mg/kg on day 1 every 21 days for 4 cycles and SBRT on cycle 2. SBRT was administered to a liver metastasis (12.5 Gy in 4 fractions) and to the right pelvis bone metastasis (4 Gy in 5 fractions) on cycle 2, days 6–11. At the end of the second cycle, imaging studies showed stable disease (RECIST 1.1). Although the CT of the soft tissue of the neck with contrast showed no recurrence, there was evidence of a prominent right lacrimal gland (Fig. 1A), which was not evident on the baseline CT scan (Fig. 1B). CT of the chest showed stable lung metastases, and increased linear ground glass opacity in the right lower lobe, which was attributed to infectious/inflammatory etiology (Fig. 2A). The patient was asymptomatic and the third dose of ipilimumab was administered. A week later, he developed edema of the right eye and arthralgia and edema in the right foot between the second and the third toes. He had no other symptoms. He was assessed by his local ophthalmologist, who diagnosed acute inflammation of the right lacrimal gland and prescribed oral antibiotics. When he returned to our clinic for the fourth cycle of ipilimumab, he complained of persistent periorbital edema of the right eye and pain in the left foot. There was no recent history of trauma. On physical examination, the right lacrimal gland was palpable without extraocular movement deficit, and with full visual fields. Fundus examination was normal. Regarding his foot, there was a palpable small, nontender, soft tissue nodule (2×2 cm) on the dorsal side of the right foot, between the second and third extensor digitorum tendons. An x-ray of the left foot revealed a benign-appearing, mildly lytic lesion at the base of the third metatarsal (Fig. 2B). A biopsy of the right lacrimal gland was performed by an ophthalmologist. Pathologic examination of multiple soft tissue fragments aggregating to 1.5×1.0×0.4 cm showed chronic inflammatory granulomatous process, negative for tumor (Fig. 3). Immune markers of the tissue were not performed. Ipilimumab was discontinued. Screening for tuberculosis [by the interferon gamma release assay (TB-spot test)], cryptococcosis [by cryptococcal antigen screening in the serum and cerebrospinal fluid (CSF)], histoplasmosis (by urinary histoplasma antigen) were negative. The immunoglobulin (Ig)G and IgM antibodies for Lyme disease were negative by immunoblot. Ig levels were normal. Antineutrophil cytoplasmic antibodies (myeloperoxidase and proteinase 3) were negative. The creatine kinase level was 64 U/L (normal; 55–170). The angiotensin-converting enzyme was below normal. C-reactive protein levels were 13.1 mg/L (normal for inflammatory conditions <13). Hepatitis B and C screening tests (hepatitis B surface antigen, hepatitis B core antibody IgM, and hepatitis C virus antibody) were negative.

Three weeks later, the patient had improvement in the periorbital edema (right) and in the edema of the left foot. It is interesting to note that he reported progressive neck muscle weakness noted with neck extension, which worsened during the day. Imaging studies

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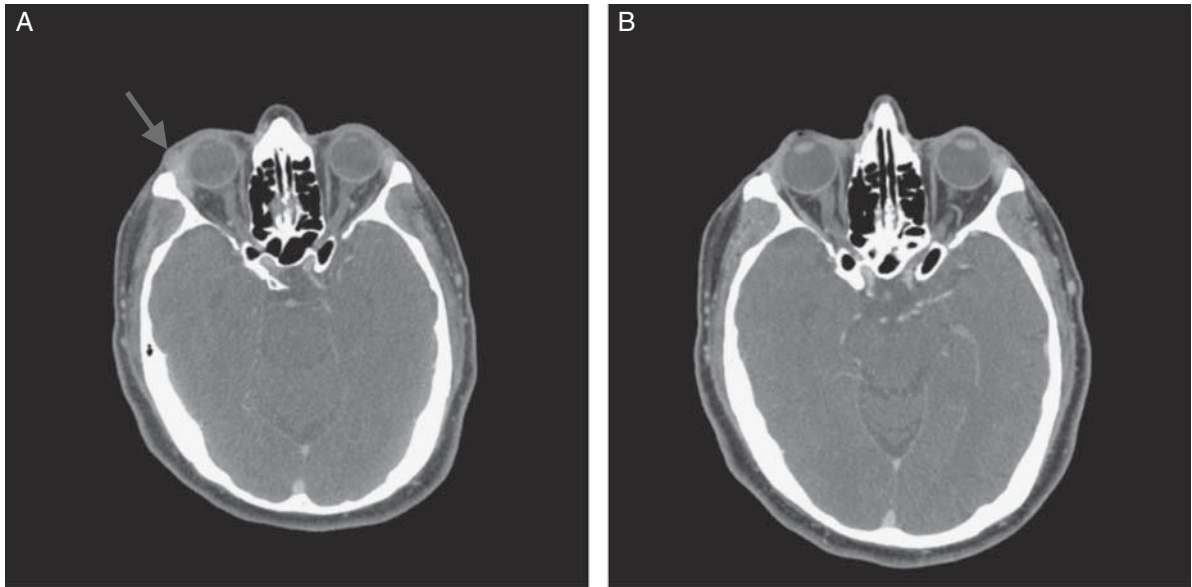


FIGURE 1. A, CT of the head and neck illustrates prominent right lacrimal gland (arrow), at the end of the second cycle of ipilimumab. B, Baseline CT of the head and neck shows normal sized lacrimal glands. CT indicates computed tomography.

showed similar findings with those at the end of cycle 2, including prominent right lacrimal gland; and overall stable disease. Work-up for myasthenic syndrome was negative for antiacetylcholine receptor antibody, and autoantibodies to muscle-specific tyrosine kinase. Electromyogram showed localized neurogenic changes in the cervical and upper paraspinal muscles, likely related to an atypical acquired axonal moderate neuritis with signs of regeneration. Thyroid profile, electroencephalogram, and CT of the head with contrast showed no abnormal findings (magnetic resonance imaging could not be

performed due to patient’s metallic implants). CSF analysis showed elevated protein (65 mg/dL; normal, 15–55), albumin (32.1 mg/dL; normal, ≤ 27.0), and IgG (10.2 mg/dL; normal, ≤ 8.1) levels. CSF Gram stain did not identify any bacteria, leukocytes, or malignant cells. The CSF culture showed no bacterial growth after 5 days. Steroids or intravenous Ig were considered, but they were not administered because the patient’s neck weakness improved with physical therapy. In June 2017, imaging studies showed resolution of linear ground glass opacity in the right lower lobe and disease

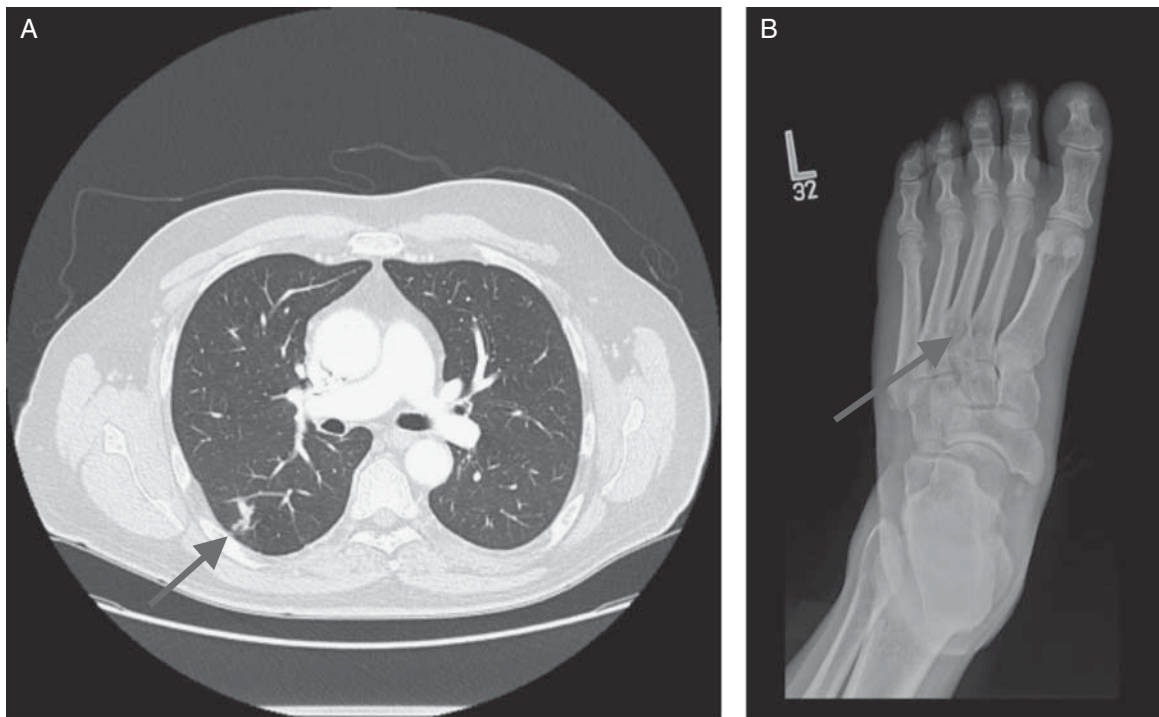


FIGURE 2. A, Computed tomography of chest showing right lower lobe ground glass opacities (arrow). B, X-ray of the left foot shows a benign-appearing, lytic lesion distorting margins at the base of the third metatarsal (arrow).

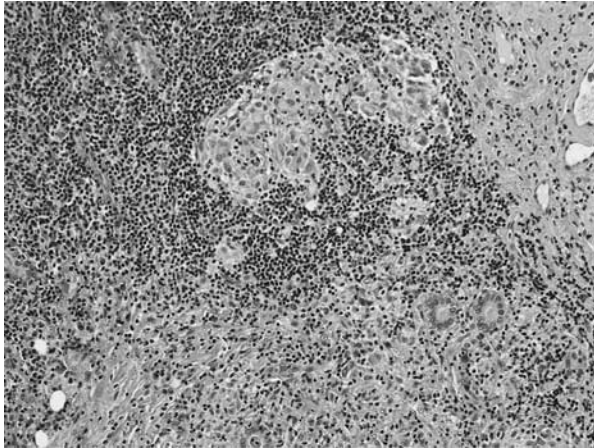


FIGURE 3. Microscopic image of the right lacrimal gland shows benign ductal proliferation and granulomatous inflammation.

progression. Subsequently, he underwent further testing for personalized cancer therapy. Cell-free tumor DNA analysis showed the same *TERT* mutation with the tumor analysis as the sole alteration. PD-L1 testing by IHC was negative (0%), the immunoperoxidase stains performed with antibodies for the DNA mismatch repair enzymes (*MSH2*, *MSH6*, *MLH1*, and *PMS2*) showed intact nuclear expression and the IHC for *PTEN* showed retained expression. All immune-related adverse events (irAEs), including neck muscle weakness resolved completely. The patient is currently participating in another early clinical trial with an histone deacetylase inhibitor.

DISCUSSION

To our knowledge, this is the first case of granulomatous lacrimal gland inflammation and axonal neuritis following treatment with immunotherapy. Although the patient's clinical presentation (granulomatous inflammation of lacrimal glands, tender subcutaneous nodule, likely erythema nodosum, and ground glass opacities in the lung) was consistent with sarcoidosis-like reaction, the work-up for infections, sarcoidosis, and vasculitis was negative. There was no evidence of malignancy in the lacrimal gland, suggesting that these events were attributed to immunotherapy, although no immune markers were performed to evaluate the clonality of the tumor-infiltrating lymphocytes. Despite the discontinuation of ipilimumab, the patient developed progressive neck weakness 6 weeks after initiation of cycle 3. Work-up for neuromuscular junction disorders, metastatic disease, and seizures was negative. Electromyogram was consistent with neuritis of the cervical and paraspinal muscles. Although symptoms could be secondary to previous exposure to radiation therapy to the neck area and resultant neuropathy/myokymia, the CSF analysis (elevated IgG, albumin, and protein levels) was consistent with an immune-mediated myopathy.

Although our patient's adverse events are mainly attributed to ipilimumab, radiation therapy may have potentiated these events. The patient was previously treated on a clinical trial with pegylated IL-10 cytokine, which was discontinued > 5 months before the described clinical presentation, making the above described events less likely associated with this treatment.

Ipilimumab, a CTLA-4 monoclonal antibody, the first checkpoint inhibitor approved by the United States Food and Drug Administration for the treatment of metastatic melanoma, is associated with various irAEs¹⁻³. The timing of adverse events is consistent with other reports showing that similar irAEs typically occur after 3 doses of

ipilimumab.⁶ Radiation therapy is associated with increased neoantigens that could prime the immune system and enhance the effect of immune checkpoint inhibitors. The combination of SBRT and ipilimumab was shown to be safe and induced response in some patients with advanced cancer excluding melanoma.⁵ All irAEs have resolved and the patient had stabilization of his disease for approximately 6 months after discontinuation of treatment.

In patients without cancer or previous treatment with immune checkpoint inhibitors, granulomatous inflammation of the lacrimal gland was found to be associated with sarcoidosis or the Wegener's granulomatosis. Of 75 patients with clinical lacrimal gland enlargement, incisional biopsy led to a diagnosis of sarcoidosis in 20% of patients (most had elevated angiotensin-converting enzyme levels) and in another series 30% were manifestations of Wegener's granulomatosis.^{7,8}

Twelve cases of sarcoidosis have been reported in patients with cancer treated with ipilimumab; however, none of the presented cases in the literature presented similar symptoms with our patient with granulomatous inflammation of the lacrimal glands and axonal neuritis.⁹⁻¹¹ The granulomatous infiltration in the context of immune checkpoint inhibitors may be attributed to lymphocytic infiltrate with CD8⁺ T cells and IL-2 secretion by activated T cells is thought to play a role in the pathogenesis of sarcoid-like granulomatous.¹²

Neurological adverse events, reported in 1%–3% of patients treated with immunotherapy,¹³ are difficult to diagnose, and potentially life threatening. These include aseptic meningitis, Tolosa-Hunt syndrome, granulomatous inflammation of the central nervous system, Guillain-Barré syndrome, transverse myelitis, and meningoradiculoneuritis.¹⁴ The first step in the management is discontinuation of immunotherapy. Most patients require steroids to reduce the intensity and duration of symptoms. Igs IV or plasmapheresis are considered in severe or steroid-refractory symptoms.¹³ Rarely, discontinuation of immunotherapy results in spontaneous resolution of the symptoms, as in our patient.

In conclusion, this case raises awareness of rare adverse events in patients treated with immunotherapy and highlights the need for early recognition and therapeutic management.

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Conflicts of Interest/Financial Disclosures

None reported. All authors have declared that there are no financial conflicts of interest with regard to this work.

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