Checkpoint inhibitor-induced sarcoi d choroidal granulomas

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ABSTRACT

Purpose: To present a novel case of sarcoi d choroidal granulomas due to nivolumab therapy for metastatic cutaneous melanoma.

Observations: A 55 year-old male with a history of stage III metastatic cutaneous melanoma treated by nivolumab presented with bilateral choroidal lesions. The ophthalmologic examination revealed bilateral creamy, yellow choroidal lesions with no ocular inflammation. The systemic workup revealed pulmonary sarcoidosis confirmed by biopsy.

Conclusion: Nivolumab is an immune checkpoint inhibitor therapy used in the treatment of metastatic melanoma. With the increasing use of immune checkpoint inhibitors in patients with advanced melanoma, clinicians should be aware of this potential associated immune-related adverse event.

1. Introduction

Immune checkpoint inhibitors (ICIs) are relatively new immunologic agents that block inhibitory receptors of the immune system including cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed death 1 (PD-1) and its ligand (PDL-1). The Food and Drug Administration-approved ICIs include the anti-CTLA-4 antibody ipilimumab, the anti-PD1 antibodies pembrolizumab and nivolumab and the anti-PDL1 antibodies atezolizumab, durvalumab and avelumab. These drugs are used for solid tumors including melanoma, non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and hematologic malignancies including Hodgkin Lymphoma. Ocular side effects secondary to ICI use are rare and occur in approximately 1% of patients. 1,2

We report the first case of sarcoi d choroidal granulomas due to nivolumab therapy for metastatic cutaneous melanoma.

2. Case report

A 55-year-old male with history of stage III cutaneous melanoma on nivolumab therapy was referred by his local ophthalmologist to the retina service for new bilateral choroidal lesions. The patient was initially diagnosed with metastatic melanoma in March 2018 when core biopsy of his right axillary lymph node revealed melanoma. He began adjuvant nivolumab therapy in May 2018 for 6 cycles and subsequently developed cough and chills.

On presentation, his uncorrected visual acuity was 20/20 in each eye. His intraocular pressure (IOP) was 13 mmHg in the right eye and 15 in the left eye. Slit lamp examination revealed no anterior or posterior intraocular inflammation. Fundus examination of the right eye revealed the presence of two creamy yellow choroidal lesions, one inferotemporal and one superotemporal to the macula. In the left eye, there was a similar lesion inferior to the arcade (Fig. 1). The retina was attached in both eyes. B-scan ultrasound showed no posterior elevation of the lesions. The differential at the time included metastatic melanoma versus choroidal granuloma.

The patient underwent chest CT in August 2018, which revealed new bulky mediastinal lymphadenopathy, hilar adenopathy and new bilateral pulmonary nodules. He underwent a biopsy that was consistent with sarcoidosis, likely caused from immunotherapy. A clinical diagnosis of choroidal granulomas due to sarcoidosis was made. Nivolumab was discontinued by his oncologist and there were no subsequent changes in the lesions.

3. Discussion

Immune checkpoint inhibitors (ICI) have transformed the treatment of melanoma and other cancers and is now part of standard management. Nivolumab is a humanized monoclonal antibody that targets the programmed cell death 1 (PD-1) receptor in T-cells. The most frequently reported adverse events of nivolumab are dermatologic, gastrointestinal and neurologic toxicity. To date, few case reports
evaluating the ocular side-effects of checkpoint inhibitors have been published. We report the first case of nivolumab-induced sarcoïd choroidal granulomas.

Cancer patients receiving ICIs are prone to develop immune-related adverse events (ICREAs) caused by non-specific activation of the host's own immune system resulting in inflammation. Ocular IREAs are rare and have been reported in less than 1% of patients. A recent review of ocular adverse events cases found that the most frequent ICI side effects included uveitis, dry eye, inflammatory orbitalopathy, and myasthenia gravis with ocular involvement. Nivolumab has been found to have the highest association with ocular myasthenia compared to other ICIs.

Several reports have described an association between the use of ICIs and the development of sarcoidosis-like reactions. In a recent comprehensive review of the literature, 55 cases were described to have developed granulomatous, sarcoïd-like lesions associated with ICIs. Ocular findings occurred in four patients and included dry-eye syndrome, acute iritis, retinochoroiditis, and panuveitis with multifocal choroiditis. Bilateral panuveitis with multifocal choroiditis was described as the first sign of systemic sarcoidosis in a patient on pembrolizumab for metastatic melanoma. The patient had pre-existing smaller and asymptomatic mediastinal and hilar adenopathy. No cases have described nivolumab-induced sarcoïd choroidal granulomas.

Sarcoïd-like reactions have been described in the setting of malignancy and have been reported during or after treatment for malignancies. It is possible that the sarcoïd choroidal granulomas may be a paraneoplastic manifestation of the patient's melanoma. One study found that 4% of melanoma patients undergoing immunotherapy developed sarcoïd-like reactions. Ocular sarcoïd-like reactions can also occur. The mechanism for these reactions remains unknown.

On initial presentation, there were bilateral creamy, yellow choroidal lesions with no elevation on B-scan ultrasound. The differential diagnosis included choroidal metastasis versus granuloma. Though cutaneous melanoma commonly metastasizes to the lymphatic system, central nervous system, liver, and lung, it accounts for only 2.2% to 4.4% of primary tumors metastasizing to the uvea. The diagnosis of choroidal granuloma due to sarcoidosis was made clinically given the new hilar adenopathy and pulmonary nodules on CT scan and the confirmatory biopsy for sarcoidosis. In addition, the patient was followed for 1 year after initial presentation with no change in the choroidal lesions.

To our knowledge, this is the first report of nivolumab-induced sarcoïd choroidal granulomas. This case illustrates that ocular sarcoidosis may be induced by nivolumab treatment. With the increasing use of ICIs in cancer patients, clinicians should be aware of this potential associated immune-related adverse event.

**Patient consent**

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.