

CASE REPORT

Systemic sarcoidosis first manifesting in a tattoo in the setting of immune checkpoint inhibition

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SUMMARY

The use of immune checkpoint inhibitors is revolutionising the treatment of cancer. However, their unique toxicity profile is substantially different from what has been observed with traditional chemotherapy, resulting in a novel learning curve for medical oncologists. Early recognition of these toxicities can make a substantial impact in ameliorating these side effects in the oncological and medical–surgical fields. Here, we present a case of Lofgren syndrome sarcoidosis, which first manifested in a tattoo in a patient with metastatic urothelial cancer on therapy with anti-CTLA-4 (ipilimumab) and anti-PD1 (nivolumab).

BACKGROUND

This case demonstrates that extrapulmonary sarcoidosis associated with immune checkpoint blockade can be mistaken for malignancy and may be misleading, resulting in premature termination of potentially efficacious treatments. Therefore, when in doubt, it is important to conduct the histopathology of metastases before discontinuation of immune checkpoint therapy.

CASE PRESENTATION

A man aged 52 years with metastatic urothelial carcinoma of the left renal pelvis was enrolled in a clinical trial with immune checkpoint therapy. He had failed prior chemotherapy with gemcitabine, paclitaxel and doxorubicin, as well as with methotrexate, vinblastine, doxorubicin and cisplatin. Approximately 60 days after beginning treatment with a combination of nivolumab (3 mg/kg intravenously) and ipilimumab (1 mg/kg intravenously), he noted papules and thickening along the black ink of two of his tattoos (figure 1). He also developed progressively enlarging papules around his eyes and nares. After three doses of immunotherapy, his restaging CT scans showed interval enlargement in the known tumour mass in the bed of kidney resection and new hilar lymphadenopathy (figure 2). Immunotherapy was discontinued due to disease progression on CT scans, and he began chemotherapy with gemcitabine and cyclophosphamide. In the mean time, he was referred to dermatology for evaluation of changes in his facial skin and tattoos.

The dermatologist performed a biopsy of a papule adjacent to his left naris, which was consistent with sarcoidosis. Special stains were negative for fungal, bacterial and acid-fast organisms. Immunohistochemistry was negative for spirochetes. Treatment with hydroxychloroquine (plaquenil) 200 mg by mouth twice

a day was initiated for sarcoidosis. After starting plaquenil, the patient reported progressive skin papules, which increased in size and number, despite discontinuation of immunotherapy.



Figure 1 Sarcoid reaction manifesting in a tattoo after immune checkpoint blockade. Thickened, hyperkeratotic papular lesions developed along the outer edges of the tattoo after the patient received ipilimumab and nivolumab combination immune checkpoint blockade therapy. Although the patient did not want the tattoo to be biopsied, histopathology of a similar nodular lesion on his left naris revealed sarcoid.

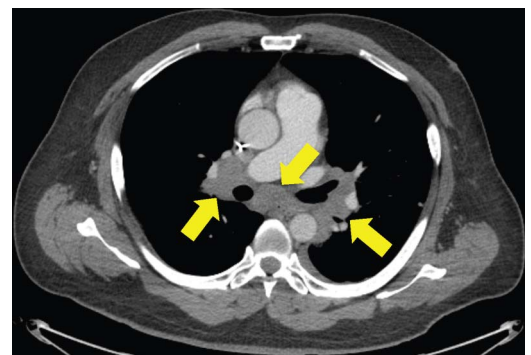


Figure 2 CT of hilar lymphadenopathy, which was initially believed to be tumour progression. After three doses of immunotherapy, restaging CT scans showed interval enlargement in the known tumour mass in the bed of kidney resection and new hilar lymphadenopathy. Immunotherapy was discontinued due to disease progression on CT scans, and he began chemotherapy with gemcitabine and cyclophosphamide. However, a hilar lymph node biopsy via bronchoscopy showed no evidence of cancer but was consistent with sarcoid.



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Systemic bloodwork was negative for hypercalcaemia, elevated ACE and elevated 1,25-dihydroxyvitamin D, which are common serum markers of sarcoidosis. However, erythrocyte sedimentation rate was elevated at 70 and 90 mm/hour (normal: <20 mm/hour) on two separate occasions. An ophthalmological examination indicated that there was no uveitis or sarcoid involvement of the eyes.

INVESTIGATIONS

The patient also experienced further induration of the black ink in his tattoos as well as tenderness and swelling of the joints of his fingers and knees. In addition, he was noted to have tender nodules anterior to his shins, bilaterally consistent with erythema nodosum. A hilar lymph node biopsy via bronchoscopy showed no evidence of cancer but was consistent with sarcoid. The diagnosis of Lofgren's syndrome was made based on the triad of hilar lymphadenopathy, arthralgias and erythema nodosum.

TREATMENT

In the light of the rapid progression of the sarcoid after discontinuation of immunotherapy, the patient was started on methylprednisolone sodium succinate (Solu-Medrol) 1 mg/kg intravenously twice a day. The skin lesions, arthralgias and tattoo changes resolved, and the patient was subsequently tapered off the steroids. Repeat CT scans (figure 3) with contrast of the chest demonstrated an increase in metastatic lesions involving the lungs and liver capsule, but a decrease in mediastinal and hilar lymphadenopathy, suggesting a clinical response of the sarcoidosis to steroids.

OUTCOME AND FOLLOW-UP

After several weeks of high-dose prednisone therapy, significant regression of the diffuse lymphadenopathy and skin lesions was seen on CT imaging studies, while the true metastatic lesions within the lung parenchyma and surgical bed remained unchanged. The patient eventually succumbed to malignancy.

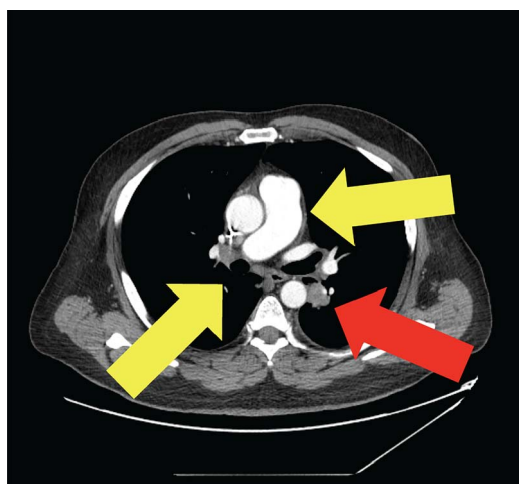


Figure 3 Methylprednisolone treatment decreased sarcoid lymphadenopathy. Methylprednisolone sodium succinate administration resolved the skin lesions, arthralgias and tattoo changes of the patient's Lofgren's syndrome. Repeat CT revealed a decrease in mediastinal and hilar lymphadenopathy (yellow arrows), suggesting a clinical response of sarcoidosis to the steroids. However, the lymphadenopathy due to malignance (red arrow) persisted.

DISCUSSION

Sarcoidosis has been reported in patients receiving immune checkpoint therapy, and has also been reported as arising from tattoos. This is the first case of sarcoid in a tattoo that occurred during the use of immune checkpoint therapy. Overall, immune checkpoint therapy has transformed the field of cancer care due to its unique ability to harness the body's antitumour immune response and yield long-lasting efficacy. Removing the cellular processes that inhibit antitumour T-cell activity has led to durable clinical responses in melanoma and genitourinary malignancies.¹⁻³ However, as demonstrated in this case, immune activation may have non-specific systemic consequences. This is especially true in disorders of immune aetiology, such as sarcoidosis, where excessive Th1 activity induces release of cytokines such as IL-2 and IFN- γ .⁴ Cutaneous and pulmonary sarcoidosis have been previously documented as drug reactions to ipilimumab, establishing a putative link between immune checkpoint blockade and the induction of sarcoidosis.⁵ Moreover, the clinical presentation of our patient reveals that the combination of ipilimumab/nivolumab can induce systemic extrapulmonary sarcoidosis in the form of Lofgren's syndrome.

We posit that immune checkpoint blockade hyperactivates the immune system and has the potential to induce pathological immune side effects. From our clinical experiences, the immune-mediated side effects of immune checkpoint blockade can be more potent than those observed with idiopathic immune dysfunction. As a result, standard therapies (such as hydroxychloroquine) that are efficacious in the non-checkpoint setting may be insufficient in reducing the significant immune infiltration and stimulation that occur in the context of immune checkpoint blockade. As shown in our report, more potent inhibition is often required to curb the adverse effects of immune checkpoint blockade, and high-dose Solu-Medrol is increasingly being used for initial management when immune checkpoint-mediated side effects occur. Although the severity of adverse effects differs on a case-by-case basis, our patient had systemic sarcoidosis and displayed an extent of immune hyperactivation that was refractory to less aggressive sarcoidosis treatments.

From a clinical perspective, it is critical to differentiate between malignant progression and immunotherapy-related sarcoidosis. We note that extrapulmonary sarcoidosis caused by immune checkpoint blockade can be mistaken for malignancy, although, in this case, the patient had known tumour progression in the bed of kidney resection as well. As a result, we emphasise the importance of conducting histopathological analyses when evaluating visceral metastases in the context of immunotherapy. Sarcoidosis is a manageable side effect and should not dictate the course of cancer treatment.

Learning points

- ▶ Early recognition of toxicities of immune checkpoint blockade can make a substantial impact in ameliorating these side effects in the oncological and medical-surgical fields.
- ▶ Immune activation due to immune checkpoint blockade therapy may have non-specific systemic consequences, such as Lofgren's sarcoidosis.
- ▶ From a clinical perspective, it is critical to differentiate between malignant progression and immunotherapy-related sarcoidosis.
- ▶ Histopathological analyses should be used to evaluate visceral metastases in the context of immunotherapy, so that sarcoidosis is not mistaken for malignancy.

Contributors CK was involved in following the patient treatment and contributed to gathering patient information, drafting the patient course, discussion, summary, background and references. AS-R was the primary oncologist and contributed to patient consent, summary, case presentation and treatment. JG contributed to case background, discussion and references. VRS was the pulmonary internist and contributed to patient care, differential diagnosis, discussion and gathering patient information.

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Competing interests None declared.

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