Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–5

DOI: 10.1177/23247096211009400
journals.sagepub.com/home/hic
SAGE

Immunotherapy-Induced Sarcoid-Like Reaction: A Shrewd Imitator

Hassaan Yasin, MD[1], Vivek Yadala, MD[1], Noman Ahmed Jang Khan, MD[1], Vincent Graffeo, MD[1], Krista Denning, MD[1], and Yehuda Lebowicz, MD[1]

Abstract

A 40-year-old male with a right-sided neck mass was diagnosed with metastatic melanoma. A repeat positron-emission tomography after treatment with combination immunotherapy demonstrated increased hypermetabolic activity in the right supraclavicular, hilar, and mediastinal regions. Immunotherapy was discontinued and a BRAF/MEK inhibitor combination was started. Repeat imaging showed a decrease in size of the neck mass; however, hilar and mediastinal lymph nodes increased in size. A fine needle aspiration of mediastinal lymph nodes was consistent with a granulomatous process. A diagnosis of a sarcoid-like reaction (SLR) was made, and he was started on steroids. A follow-up positron emission tomography showed decreased hilar and mediastinal lymph node hypermetabolic activity. We, therefore, report this rare case of immunotherapy-induced SLR to the expanding literature on immunotherapy-related adverse effects and would like to highlight that SLR can occur in conjunction with disease progression making it challenging to distinguish between the two.

Keywords

sarcoid-like reaction, sarcoidosis, immunotherapy, melanoma, ipilimumab, nivolumab

Background

The advent of immunotherapy has revolutionized the treatment paradigm of cancer treatment, and though less toxic compared with standard chemotherapy agents, it is associated with a distinct group of side effects referred to as immune-related adverse effects.[1] These adverse effects are most commonly seen in patients receiving ipilimumab/nivolumab combination therapy.[1] The organs most commonly involved include the gastrointestinal tract, liver, endocrine glands, and the skin.[2] Sarcoid-like reaction (SLR) is a rare but an important immune-related adverse effect as it may mimic disease progression and pose a major diagnostic dilemma.[3] We report a case of sarcoid-like granulomatous reaction that occurred in conjunction with disease progression in a patient with malignant melanoma, after treatment with programmed death-1 inhibitor (PDL-1) nivolumab, in combination with cytotoxic T-lymphocyte-associated antigen-4 inhibitor (CTLA-4) ipilimumab, making it a challenge to distinguish between the two.

Case Presentation

A 40-year-old gentleman was referred to our clinic for evaluation of a right-sided neck swelling. The swelling had progressively increased in size over a 6-month period and was associated with fatigue and malaise. The rest of the review of systems was negative. Past medical history was significant for uncontrolled diabetes mellitus type 2, hypertension, hyperlipidemia, chronic kidney disease, and tobacco use. Vital signs were stable, and physical examination disclosed an approximately 4 cm nontender, nonfluctuant, firm oval swelling in the posterior triangle of the neck on the right, and multiple nevi on the back. All initial laboratory tests including complete blood count, chemistry, thyroid profile, and liver function were within normal limits, except for a serum creatinine of 1.8. A computed tomography (CT) scan of neck showed a 2.1 × 2.1 × 2.7 cm sized oval mass on the right, presumably an enlarged lymph node, which was suspicious for malignancy. A whole-body positron emission tomography (PET) showed only a hypermetabolic mass in the lower posterior triangle of the right neck (Figure 1). A magnetic resonance imaging of the brain with contrast demonstrated a

[1]Marshall University, Huntington, WV, USA

Received March 5, 2021. Revised March 15, 2021. Accepted March 18, 2021.

Corresponding Author:
Hassaan Yasin, MD, Marshall University Joan C. Edwards School of Medicine, 1400 Hal Greer Boulevard, Huntington, WV 25701, USA.
Email: hassaan_habib@hotmail.com

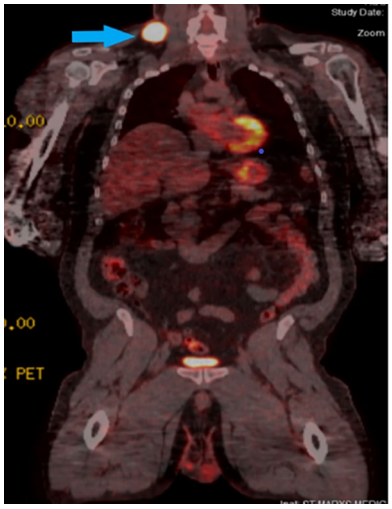

Figure 1. A whole-body positron emission tomography showing a hypermetabolic mass in the lower posterior triangle of the right neck (blue arrow).

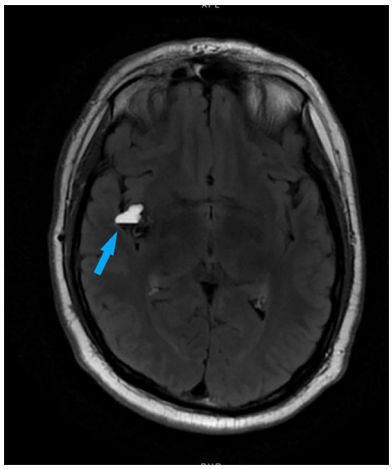

Figure 2. Magnetic resonance imaging of the brain with contrast showing a 2-cm mass in the right temporal lobe (blue arrow).

2-cm mass in the right temporal lobe (Figure 2). An ultrasound-guided fine needle aspiration of the mass revealed malignant cells but pathologic examination could not differentiate the cell type. An excisional biopsy of the mass was subsequently performed. Immunohistochemistry stains on tumor cells were positive for SOX-10, vimentin, and S-100, and negative for cytokeratin AE1/AE3, cytokeratin 5/6, p63, p16, CAM 5.2, EMA, CD45, CD56, CD34, smooth muscle actin, and desmin (Figures 3 and 4). The differentials reported by our pathologist included malignant melanoma and malignant peripheral nerve sheath tumor. The pathology was reviewed at Johns Hopkins University and a diagnosis of

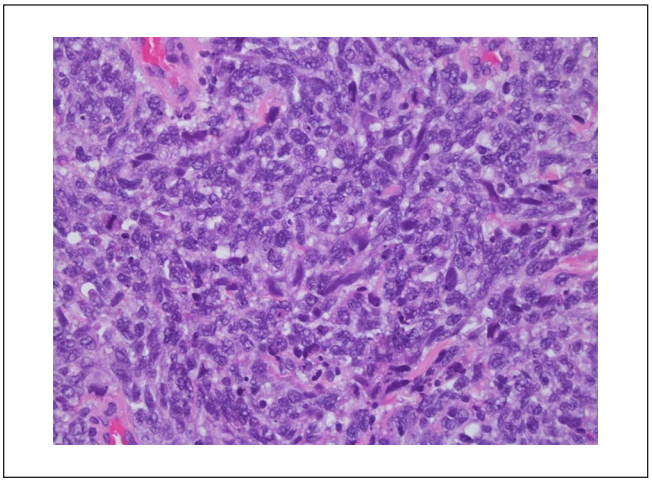

Figure 3. Pathology from excisional biopsy of the mass with hematoxylin and eosin stain showing tightly packed pleomorphic malignant cells with prominent mitotic activity and necrosis.

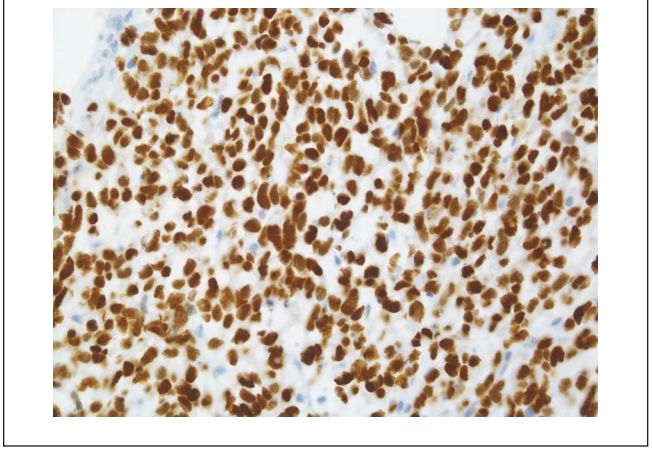

Figure 4. Immunostaining with SOX-10 positive in the tumor cell nuclei.

malignant melanoma was suggested. The patient initially underwent stereotactic radiosurgery for the solitary brain metastases. He was then started on a PDL-1 inhibitor, nivolumab. A cytotoxic T-lymphocyte associated protein, ipilimumab, was added after 4 cycles to potentially achieve a better response since the neck mass remained palpable. A repeat whole-body PET/CT after 7 cycles of treatment demonstrated an increase in hypermetabolic activity in the right supraclavicular area and development of hypermetabolic activity in the infraclavicular, hilar, and mediastinal regions (Figure 5). A next-generation sequencing analysis was positive for BRAF V600E mutation. Therefore, combination immunotherapy was stopped, and the patient was started on a combination BRAF/MEK inhibitor therapy. Laboratory values on a subsequent follow-up visit revealed a serum calcium level of 13.3. Further workup revealed a low

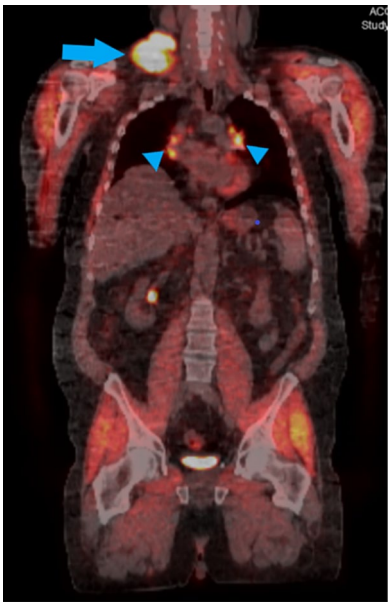

Figure 5. Repeat whole body positron emission tomography after 7 cycles of treatment showing an increased hypermetabolic activity in the right supraclavicular area (blue arrow) and new hypermetabolic activity in the mediastinal and hilar lymph nodes (arrow heads).

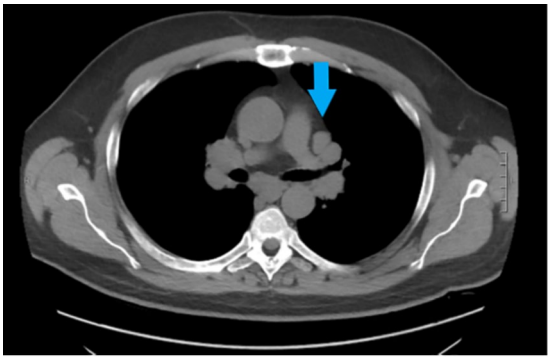

Figure 6. A repeat computed tomography of the chest after 2 months of treatment with BRAF/MEK inhibitor showing an enlarged mediastinal lymph node (blue arrow).

parathyroid hormone level, a high normal calcitriol level, and an elevated angiotensin-converting enzyme (ACE) level. Other laboratory findings including parathyroid hormone-related peptide, cortisol, thyroid studies, and liver function tests were unremarkable. A repeat CT after 2 months of treatment with the combination BRAF/MEK inhibitors showed a significant decrease in size of the neck mass; however, mediastinal and hilar lymph nodes had increased in size (Figure 6). With an elevated serum calcium level and a mixed response

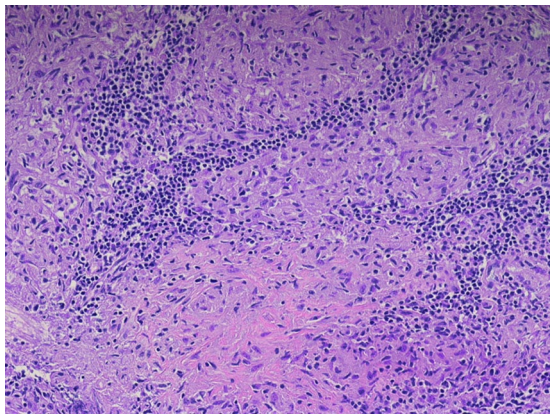

Figure 7. Pathology from fine needle aspiration of mediastinal lymph node with hematoxylin and eosin stain showing giant cells, epithelioid histiocytes, and lymphocytes are present, consistent with granulomatous process.

on imaging, there was suspicion for an underlying granulomatous disease. He subsequently underwent bronchoscopy and the pathology from the fine needle aspiration of the enlarged mediastinal lymph node showed giant cells, epithelioid histiocytes, and lymphocytes consistent with a granulomatous process, and no malignant cells were found (Figure 7). Also to note, bronchial washing was negative for *Mycobacterium* or fungal infection. A diagnosis of immunotherapy-induced SLR was made. He required a brief hospitalization for hypercalcemia and acute on chronic renal failure, and was treated with intravenous bisphosphonates, hydration, and was started on steroids. Subsequent laboratory tests revealed normalization of Ca (9 mg/dL) and ACE levels (<15 U/L). On subsequent follow-ups, he showed radiological improvement suggested by PET scan, and CT scans of chest (Figure 8).

Discussion

Sarcoid-like reactions are granulomatous reactions that differ from systemic sarcoidosis by their lack of multisystem organ involvement and are being increasingly observed with modern melanoma therapy.[4] They have been reported to occur in 5% of patients treated with immune check point inhibitors and thus far only a few cases have been reported.[5] In the literature, the most common malignancy associated with SLR is melanoma, and the most common immune checkpoint inhibitor is ipilimumab.[6] The time to onset of SLR after initiation of immune checkpoint inhibitors (ICIs) can range from 3 weeks to almost 2 years.[6]

The underlying pathophysiology of SLR is not yet fully understood. One of the mechanisms proposed is that anti-CTLA activity and PD-1 pathway blockade increases

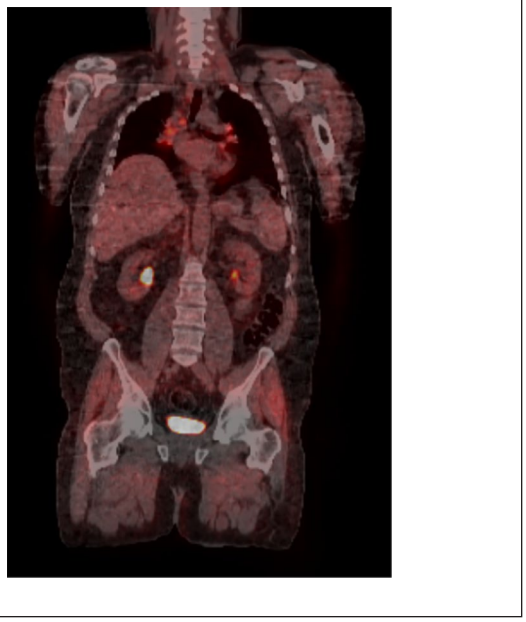

Figure 8. A follow-up whole body positron emission tomography after treatment with the combination BRAF/MEK inhibitor and corticosteroids showing resolution of hypermetabolic lymph nodes.

T-helper 17 cell function, thereby stimulating an increased production of a pro-inflammatory cytokine, interleukin 17, which is capable of inducing a strong autoimmune response.[6] This is supported by evidence that patients with sarcoidosis have an increased ratio of T-helper 17 cells to T-regulatory cells in the peripheral blood and the bronchoalveolar lavage.[7] Our patient did not have a prior history of sarcoidosis, and it remains unclear if immunotherapy had unmasked a preexisting condition, or had in fact caused immune disruption leading to new sarcoidosis-like granulomatous lesions.

SLR most commonly occurs in the lungs, and typically present with pulmonary nodules and mediastinal lymphadenopathy that can demonstrate nonspecific ^{18}F-fluorodeoxyglucose uptake.[5,8] There is no set standardized uptake value that can distinguish SLR from malignant uptake. They can therefore mimic disease progression and lead to an inadvertent change in treatment. In our patient, disease progression and development of a SLR occurred concomitantly, presenting an incredibly unique dilemma. In such a scenario if SLR remains undiagnosed, it can lead to an inaccurate assessment of tumor response with subsequent imaging as well as lead to debilitating complications such as hypercalcemia-induced renal failure. Therefore, treating physicians should keep SLR in consideration as a differential diagnosis particularly in the presence of mediastinal lymphadenopathy and hypercalcemia. Though hypercalcemia is seen in only 11% of patients with sarcoidosis[9] and elevated serum ACE levels lack sensitivity and specificity,[10] checking for serum calcium and ACE levels may aid in raising or alleviating the degree of suspicion of SLR. A tissue biopsy is indispensable in such cases and should be obtained to establish a definitive diagnosis. On histopathology, ICI-induced SLR is like sarcoidosis and is characterized by noncaseating giant cell and epithelioid granulomas.[4]

Treatment of ICI-induced SLR invariably involves discontinuation of checkpoint inhibitors.[11] Not all patients with ICI-induced SLR need treatment with corticosteroids. Corticosteroids are indicated if there are significant symptoms or evidence of organ damage. There have been no cases reported to date that were refractory to discontinuation of ICI or treatment with corticosteroids.

Conclusion

ICI-associated SLR is a rare but an important immunotherapy-related adverse effect. SLR associated with ICIs cannot be radiographically distinguished from disease recurrence and can prompt an unwarranted change in treatment. Our case serves to highlight that SLR can also occur in conjunction with disease progression making it an even bigger dilemma to distinguish between the two.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information including facial images to be published in this article.

References

1. Kaehler KC, Piel S, Livingstone E, Schilling B, Hauschild A, Schadendorf D. Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns, immune-related adverse events, and their management. *Semin Oncol*. 2010;37:485-498.
2. Xing P, Zhang F, Wang G, et al. Incidence rates of immune-related adverse events and their correlation with response in advanced solid tumours treated with NIVO or NIVO+ IPI: a systematic review and meta-analysis. *J Immunother Cancer*. 2019;7:341.
3. Tetzlaff MT, Nelson KC, Diab A, et al. Granulomatous/sarcoid-like lesions associated with checkpoint inhibitors: a

marker of therapy response in a subset of melanoma patients. *J Immunother Cancer*. 2018;6:14.
4. Dimitriou F, Frauchiger AL, Urosevic-Maiwald M, et al. Sarcoid-like reactions in patients receiving modern melanoma treatment. *Melanoma Res*. 2018;28:230-236.
5. Nishino M, Sholl LM, Awad MM, Hatabu H, Armand P, Hodi FS. Sarcoid-like granulomatosis of the lung related to immune-checkpoint inhibitors: distinct clinical and imaging features of a unique immune-related adverse event. *Cancer Immunol Res*. 2018;6:630-635.
6. Gkiozos I, Kopitopoulou A, Kalkanis A, et al. Sarcoidosis-like reactions induced by checkpoint inhibitors. *J Thorac Oncol*. 2018;13:1076-1082.
7. Huang H, Lu Z, Jiang C, Liu J, Wang Y, Xu Z. Imbalance between Th17 and regulatory T-cells in sarcoidosis. *Int J Mol Sci*. 2013;14:21463-21473.
8. Gaughan EM. Sarcoidosis, malignancy and immune checkpoint blockade. *Immunotherapy*. 2017;9:1051-1053.
9. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med*. 2007;357:2153-2165.
10. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic utility of angiotensin-converting enzyme in sarcoidosis: a population-based study. *Lung*. 2016;194:91-95.
11. Cousin S, Toulmonde M, Kind M, et al. Pulmonary sarcoidosis induced by the anti-PD1 monoclonal antibody pembrolizumab. *Ann Oncol*. 2016;27:1178-1179.