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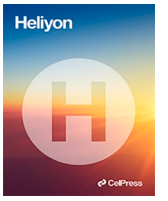

Case report

Sarcoid-like reaction in malignant melanoma exacerbated with pembrolizumab therapy case report☆,☆☆

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ABSTRACT

Sarcoid Like Reaction (SLR) is a localized non-caseating epithelioid granulomatous reaction seen secondary to certain immunotherapies and malignancies. Invasive melanoma, while being associated with onset of sarcoidosis, has not shown to directly induce SLR in the literature. We present the case of a 68-year-old male with malignant melanoma, who was found to have SLR prior to starting immunotherapy, which worsened while on pembrolizumab. This case highlights the challenge of distinguishing between drug-induced SLR and melanoma-induced SLR, and the implications in terms of management.

1. Introduction

Sarcoid like reactions (SLR) consists of a localized reaction with histopathological finding of noncaseating epithelioid cell granulomas. While the exact pathophysiology underlying SLR is unclear, studies suggest that it is attributed to diverse antigens that are coupled with genetic susceptibility, thus triggering T cell mediated immune responses and leading to the formation of noncaseating epithelioid cell granulomas [1].

In the context of melanoma, many case studies have reported the relationship between invasive melanoma and the onset of sarcoidosis, but there have been no significant reports of SLR secondary to melanoma [2,3]. On the other hand, the development of SLR has been documented with the use of certain immunotherapies for the treatment of malignant melanoma such as BRAF inhibitors, MEK

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inhibitors, and pembrolizumab [4,5]. This report presents a case of a patient with malignant melanoma that was found to have the diagnosis of SLR secondary to melanoma which was exacerbated after the initiation of pembrolizumab. This is significant because of the implications regarding management vary between drug-induced or melanoma-induced SLR.

2. Case presentation

A 68-year-old male presented to the dermatologist office for evaluation of pigmented lesions on the left lower extremity. He received a shaved biopsy with pathology showing evidence of locally advanced invasive malignant melanoma. As part of his preoperative work-up, he received a chest x-ray which showed no evidence of masses. Shortly after, the patient went for wide surgical resection of the tumor along with three sentinel nodes biopsies, which showed no residual malignancy.

Prior to the initiation of immunotherapy, the patient had a PET CT scan which showed hypermetabolic mediastinal lymphadenopathy extending into the bilateral hila and supraclavicular regions (Fig. 1a and b). A standardized uptake value (SUV) of 17.8 was found on PET CT scan, necessitating biopsy to rule out metastasis. During the mediastinoscopy, two anterior mediastinal lymph nodes were biopsied which revealed chronic non-necrotizing granulomatous inflammation, but were negative for malignancy. Consequently, the patient was referred to pulmonology due to concern of sarcoidosis. He was found to be asymptomatic on presentation. Extensive lab work including an ACE level, ANA screen, double-stranded antibody, CRP, ESR, SCL-70, rheumatoid factor, IgE, IgG, and myositis related antibodies were negative. An echocardiogram showed a preserved EF, with normal left ventricle size, and no overt valvular pathology. ECG, echo and PET scan findings showed no evidence to suggest cardiac sarcoidosis. A discussion about family history revealed patient's mother had a history of pulmonary hypertension, but patient denies any personal history of pulmonary issues. Pulmonary function tests showed evidence of early airway obstruction with FEV1/FVC of 67 % (FEV1 of 76 % and FVC of 114 %) with improvement in mid flows after inhaled bronchodilator therapy. The DLCO was in normal reference range (117 % predicted). The patient was also seen by an ophthalmologist for a slit-lamp test that demonstrated no evidence of anterior uveitis or sarcoid related lesions. The patient did not fulfill the systemic requirements for sarcoidosis, suggesting a diagnosis of SLR.

The patient followed up with his oncologist who started him on adjuvant chemotherapy with pembrolizumab. Two weeks after his first treatment with pembrolizumab, the patient received a high-resolution CT chest which revealed worsening mediastinal and hilar adenopathy compared to the previous CT (Fig. 2a and b). It is not clear if this change was secondary to the initiation of Pembrolizumab, or another etiology, but no suspicious lung mass or evidence of infiltrate was identified. During the second workup for the worsening adenopathy, the patient continued to be asymptomatic with no new clinical complaints or new physical exam findings. The patient had received a total of four cycles of pembrolizumab therapy before it was discontinued. The patient was transitioned to 40 mg Prednisone daily which he took for six weeks. The patient was later rechallenged with pembrolizumab therapy, with repeat PT-CT scans showing improvement in his mediastinal lymphadenopathy. Patient continued to be asymptomatic, and clinically felt well, with an encouraging prognosis, as metastasis was local.

3. Discussion

While previous case reports have shown a link between pembrolizumab and the induction of a SLR, there is little data to show a similar correlation with melanoma induced SLR. This case report demonstrates a SLR manifesting as mediastinal lymphadenopathy, prior to starting pembrolizumab. This presentation suggests that the SLR was likely secondary to the melanoma itself. The finding of the initial mediastinal lymphadenopathy prior to starting pembrolizumab was found incidentally during the staging process of the melanoma. Had this imaging study not been done, it is likely that any future findings of biopsy proven SLR would have been attributed to the start of immunotherapy. With the start of the immunotherapy the lymphadenopathy worsened, which is a finding concordant with previous literature. One diagnostic challenge and limitation in our case report is that we did not have access to a previous CT prior to the incidence of the melanoma. This may suggest that an SLR was occurring concurrently with the melanoma, but without a strong family or personal history of autoimmune disease or sarcoidosis, it is likely that the SLR was secondary to another process. This raises the question of whether the incidence of melanoma induced SLR is underreported in the current literature, as it may be masked by the drug-induced SLR from the immunotherapy.

Interestingly, some studies suggest that SLR may have a protective effect by provoking an immune response against the malignancy.

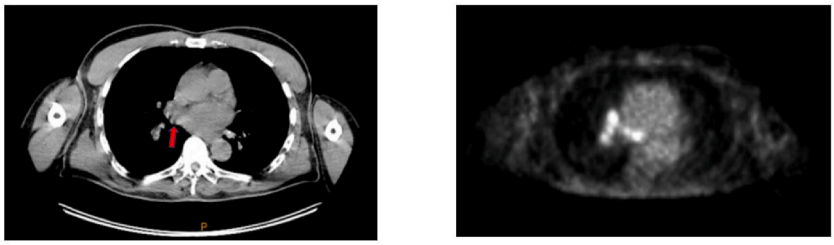

Fig. 1. This figure shows evidence of mediastinal lymphadenopathy extending into bilateral hila prior to starting Pembrolizumab therapy. Fig. 1a CT evidence of mediastinal lymphadenopathy at the corresponding level while Fig. 1b shows the lymphadenopathy via PET scan.

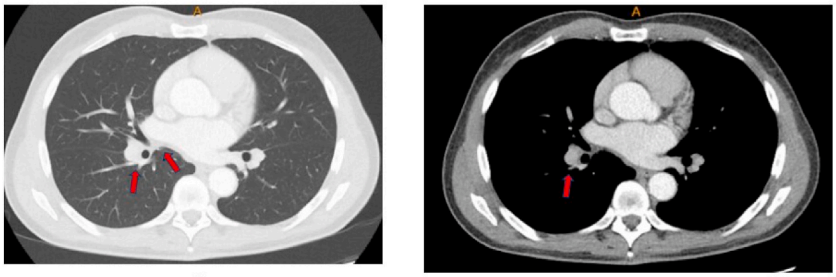

Fig. 2. Two weeks after starting Pembrolizumab, the patient had a repeat CT showing worsening lymphadenopathy. As can be seen, in Fig. 2a and b, the patient has marked hilar adenopathy.

For instance, in subjects with SLR and non-small cell lung cancer (NSCLC), there was a significantly greater cancer-free survival period compared to the controls [6]. In another study, among patients with skin, breast, prostate cancers, and lymphoma, there was decreased occurrence of stage 4 cancer in patients with SLR compared to controls [7,8]. It is not clear whether a similar relationship would be seen with melanoma-induced SLR, or if the protective effects, would persist if it was drug-induced. This is significant, because the approach to treatment for SLR depends on the etiology. Current guidelines recommend either temporarily holding or permanently stopping pembrolizumab in the case of drug induced SLR, as it will often lead to remission of the SLR [9]. In SLR secondary to cancer, treating the underlying malignancy using the immunotherapy would lead to the remission of the SLR, which was seen in the second rechallenge of pembrolizumab therapy in our case. Thus, if the incidence of SLR secondary to melanoma is being underreported or misattributed to pembrolizumab induced SLR, then current management guidelines would need to be modified to reflect this new hypothesis.

4. Conclusion

- This presentation suggests that the SLR was likely secondary to the melanoma itself, rather than secondary to pembrolizumab.
- What remains unclear is if the current literature underestimates the effects of malignancies such as melanoma in contributing to the development of SLR, or if it can be truly attributed to being mostly drug-induced
- There is also a question on whether there is a difference in prognosis of SLR, depending on whether it is malignancy induced or drug-induced, and how this would change management options in the future.

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CRediT authorship contribution statement

Mohammed Ahsan: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Conceptualization. **Alex Ashkin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Conceptualization. **David H. Lindner:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Investigation, Formal analysis, Conceptualization. **Vishal P. Patel:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Andrew Lipman:** Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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