Sarcoid-Like Reaction Mimicking Disease Progression Associated with Nivolumab in a Case with Malignant Mesothelioma: Is There a Solution for This Dilemma?

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Abstract
Sarcoid like reaction is an interesting entity in cases treated by checkpoint inhibitor treatment and suggests a good response to therapy. Here a case with granulomatous reaction has been reported in a case with malignant mesothelioma treated by nivolumab. This entity may simulate disease progression by imaging modalities especially in PET/CT.

Keywords: Sarcoid like granulomatous reaction, checkpoint inhibitor, malignant mesothelioma

Case Report
A 53-year-old woman was admitted with pleural malignant mesothelioma (MM) epithelioid type. After surgery, pemetrexed–cisplatin and bevacizumab was given for 6 cycles and bevacizumab maintenance for 10 cycles. Vinorelbine was given for 4 cycles for progressive disease. There was a partial response at the end of 8 cycles. Positron emission tomography/computed tomography (PET/CT) showed considerable progression and carboplatin–gemcitabine combination was given. There were metabolic nodules at the left lung, and pleural thickening and soft tissue masses were found in PET/CT (Fig. 1). Due to an active tumor and severe pains, nivolumab was given for 6 cycles. Her general condition was excellent, and she did not require analgesics. However, PET/CT showed considerable progression (Fig. 2). Her condition was very well and post-immunotherapy granulomatous inflammation was considered clinically. Biopsy was performed from a pelvic lymph node and was reported as MM metastasis. She had no other treatment choice, and therefore salvage surgery was performed: omentectomy, paraaortic and coeliac lymphadenectomy, right (6/11) and left pelvic lymphadenectomy, diaphragm...
resection, pulmonary parenchymal resection, pleurectomy, and pericardiectomy were performed. All of the tissue samples except 6 of 17 right pelvic lymph nodes and paraaortic lymph nodes were reported as granulomatous reactions. Figures 3 and 4 show granulomas.

Discussion

Checkpoint inhibitors (CPIs) have various adverse events, but SLR is a relatively little known reaction in cases treated by CPIs. SLRs may mimic disease progression and may cause discontinuation of the useful therapies.\(^1\)\(^2\) It is well known that CPI-related adverse effects are generally associated with favorable clinical outcomes, and it has been suggested, at least in some reports, that SLR is associated with a better outcome. Also sarcoid-like reactions associated with CPIs have been found to be better responses to therapy.\(^3\) There is no specific recommendation for patients developing SLR during CPI treatment: asymptomatic patients do not require treatment, and symptomatic cases respond to steroids. If there is no response to steroids, other immunosuppressives may be used.\(^3\)\(^4\)

In our case, there was clear evidence of progression at PET/CT but her clinical condition was excellent. At this point, a granulomatous reaction was preferred, but biopsy showed MM, and therefore brutal surgery was performed. However, the majority of the surgical specimens showed a granulomatous reaction, while only paraaortic and one-third of right pelvic lymph nodes showed the tumor. Clinicians should be aware of SLRs in cases treated by CPIs, and tissues must be sampled and reviewed by an experienced pathologist to avoid misdiagnosis and drug stops while responding to the tumor.\(^1\) In clinical practice, fluorodeoxyglucose (FDG) PET/CT is the most frequently used imaging technique to measure the response to CPIs but is not sensitive enough to predict atypical immune-related adverse events including pseudoprogression and SLR. Newer imaging modalities including 18F-fluorothymidine (FLT) PET imaging may be useful. It is known that FLT is a substrate for thymidine kinase which is transported into the cell during DNA synthesis and trapped, but not incorporated into the DNA. It has been hypothesized that FLT PET is an important tool to show the proliferative activity of the tumor and has advantages to detect and differentiate tumor progression from pseudoprogression associated with tumor-infiltrating immune cells which have low proliferative capacity than tu-

![Figure 1. PET/CT imaging before nivolumab.](image1)

![Figure 2. PET/CT imaging after nivolumab.](image2)
By analogy, it can be proposed that FLT/PET may be used in cases with good clinical outcomes in spite of progression detected by FDG/PET.

The clinical outcome of the patient is very interesting:
1. The patient responded to CPI treatment at a fourth-line setting.
2. PET CT imaging showed progressive findings due to granulomatous reaction.

It can be said that SLR is not a rare event in cases treated with CPIs, and awareness of these reactions will save the patients from unnecessary procedures and allows the patients to continue useful treatment. Newer PET/CT imaging modalities may be useful to differentiate SLR from progressive disease.

Disclosures
Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.
Conflict of Interest: None declared.


References