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PII: S1556-0864(18)30593-8

DOI: 10.1016/j.jtho.2018.04.031

Reference: JTHO 963

To appear in: *Journal of Thoracic Oncology*

Received Date: 22 January 2018

Revised Date: 29 April 2018

Accepted Date: 30 April 2018

Please cite this article as: Gkiozos I, Kopitopoulou A, Kalkanis A, Ioannis VN, Judson MA, Syrigos KN, Sarcoidosis-like reactions induced by checkpoint inhibitors, *Journal of Thoracic Oncology* (2018), doi: 10.1016/j.jtho.2018.04.031.

Sarcoidosis-like reactions induced by checkpoint inhibitors.

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Key Words: checkpoint inhibitors, immune-related adverse events, sarcoidosis-like reactions

DISCLOSURES:

Dr. Vamvakaris has nothing to disclose.

MAJ is a consultant for Biogen. His institution has received grants from Mallinckrodt Pharmaceuticals and Novartis.

Dr. SYRIGOS reports grants from LILLY, grants from BOEHRINGER INGELHEIM, grants and personal fees from BRISTOL MYERS SQUIBB, grants from MERCK SARONO, grants and personal fees from ROCHE, personal fees from BAYER, personal fees from ASTRA ZENECA, personal fees from MSD, outside the submitted work.

Dr. KOPITOPOULOU reports personal fees from BRISTOL MYERS SQUIBB, outside the submitted work.

Dr. GKIOZOS reports personal fees from BOEHRINGER INGELHEIM, personal fees from BRISTOL MYERS SQUIBB, personal fees from ROCHE, outside the submitted work.

Dr. Kalkanis has nothing to disclose.

Introduction

Several drugs have been associated with the development of syndromes indistinguishable from sarcoidosis that are described as “sarcoidosis-like reactions.” Since the exact immunopathogenesis of sarcoidosis is unknown, it is not clear if these drugs are truly causing sarcoidosis, rendering the immune system more susceptible to the development of sarcoidosis, or are distinct entities from sarcoidosis. Drugs associated with sarcoidosis-like reactions include interferon-α[1-3], highly active anti-retroviral therapy (HAART),[4-6] and tumor necrosis factor alpha antagonists.[7-10]

Immunotherapy is a newly developed component of cancer care that expands the treatment possibilities for patients. Unfortunately, immunotherapy may also generate toxicities related immune system dysregulation and/or stimulation called immune-related adverse events (irAEs). IrAEs may potentially affect any tissue,[11] and may manifest as a sarcoidosis-like reaction, reactive lymphadenopathy, dermatological manifestations such as plaques and nodules, gastrointestinal manifestations such as colitis and endocrine deregulation including hypophysitis and hypothyroidism.[12]

Without performing a tissue biopsy, it may be problematic to differentiate a sarcoidosis-like reaction from an alternative cause of an irAE. For example, although a sarcoidosis-like reaction may cause mediastinal lymphadenopathy on chest imaging, an identical radiographic appearance may occur from an irAE causing reactive lymphadenopathy in mediastinal lymph nodes.[13]

Although biopsies are not always performed to establish if an irAE represents a sarcoidosis-like reaction as opposed to other forms of irAEs, they are often indicated to exclude infectious or malignant processes that may have similar clinical presentations to irAEs.

Recently, several reports have described an association between the use of immune checkpoint inhibitors (ICIs) and the development of sarcoidosis-like reactions. ICIs inactivate proteins that have been synthesized by immune cells such as T-lymphocytes as well as tumor cells that inhibit antitumor T- cell activity.[14] Inactivation of these proteins by ICIs has led to durable clinical responses in several malignancies.[15] However, ICI-induced activation of the immune system may have additional consequences, including the development irAEs and specifically, sarcoidosis-like reactions. In this manuscript, we review the evidence for the association of ICI therapy and the development of sarcoidosis-like reactions, discuss the potential mechanisms for this association, and explore how this association may provide insights into the pathogenesis of sarcoidosis.

Proposed mechanisms of checkpoint inhibitors causing sarcoidosis-like reactions.

Ipilimumab is a humanized monoclonal antibody directed against cytotoxic T-

lymphocyte antigen-4 (CTLA-4) that is approved for the treatment of metastatic melanoma and has been shown to increase survival in these patients.[16] Blockade of CTLA-4 is thought to elicit an antitumor immune response by overcoming CTLA-4 mediated T-lymphocyte suppression. Consequently, it prolongs T-cell activation and restores T-cell proliferation, thus amplifying T-cell-mediated immunity and the capacity of the patient to mount an effective antitumor immune response.[17] Recent data suggest that in patients with melanoma, ipilimumab can enhance both immune responses and humoral immunity mediated by different T-cell populations.[18]

The clinical response to ipilimumab has been shown to correlate with a subsequent, treatment-induced increase in lymphocyte counts[19] and an increased expression of Th1-associated markers.[20] The emergence of lymphocytes with an increased expression of Th1-associated markers could potentially induce a sarcoidosis-like reaction, as these cells are abundant in active sarcoidosis and thought to be integral to the development of the sarcoid granuloma.[21]

Another proposed mechanism for ICI-induced sarcoidosis-like reactions involves an increase in the number and function of Th17 cells that has been demonstrated in melanoma patients who received anti CTLA-4 treatment.[25,26] Th17 cells are thought to have an integral role in the development of sarcoid granulomas and may also promote the development of sarcoidosis induced fibrosis.[22] In addition, there is evidence of a T17 cell – T regulatory cell (Treg) imbalance in sarcoidosis, with an increased T17/Treg ratio both in the

peripheral blood and bronchoalveolar lavage fluid of sarcoidosis patients.[23] Additionally, a recent large case-control study confirmed an association between genetic variants near the IL-23 receptor (which promotes Th17 responses) in different cohorts of subjects with sarcoidosis.[24]

Immune checkpoint antibodies that inhibit the programmed cell death protein 1 (PD-1)/PD-Ligand 1 pathway have demonstrated antitumor activity against numerous malignancies, and recently gained regulatory approval as single-agent therapy for the treatment of metastatic malignant melanoma and non-small cell lung cancer.[27] Inhibitory receptor PD-1 and its ligand, PD-L1, also appear to play a role in the immunopathogenesis of sarcoidosis. Braun and coworkers demonstrated that increased numbers of PD-1+CD4+ T cells are present in the blood compartment and BAL of pulmonary sarcoidosis patients.[28] Additionally, PD- L1 has been shown to be up-regulated in sarcoid lung granulomas but not in healthy lung tissue. Furthermore, in vitro blockade of the PD-1 pathway restored the proliferative capacity of sarcoidosis CD4+ T cells to levels consistent with healthy control subjects. Because of this established association of PD-1 and PD-L1 and the granulomatous inflammation of sarcoidosis, it seems paradoxical that checkpoint inhibitors that block PD-1 and PD-L1 have been shown to potentiate the T helper-1 T-cell-mediated response and cause sarcoidosis. It has been postulated that this paradoxical response may involve IL-17–producing cells, including CD4+ Th17 cells, that are known to be expanded in sarcoidosis.[29] Researchers have shown an association between the presence of abnormally high numbers of circulating Th17.1 cells in melanoma patients prior to receiving anti-

programmed cell death-1 antibody therapy and the onset of sarcoidosis.[30] This suggests that anti-programmed cell death-1 antibody therapy may amplify the effects of Th17.1 cells to cause sarcoidosis.

Clinical presentation of sarcoidosis-like reactions: time course for drug initiation, phenotypic expression, clinical course.

Table 1 shows the currently reported cases of sarcoidosis-like reactions associated with the use of ICIs. The most common ICI associated with sarcoidosis-like reactions is ipilimumab, although cases have been reported with nivolumab, pembrolizumab, and anti-PD-L1 antibody therapy. Most of the underlying malignancies have been melanoma, which probably relates to the clinical indication for ICI use. ICI-related sarcoidosis-like reactions have also been reported in patients with prostate carcinoma, Hodgkin's lymphoma, and uterine leiomyosarcoma. The time to onset of sarcoidosis-like reactions after initiating ICIs has ranged from 3 weeks to almost two years, although all cases except one occurred within 36 weeks.[33] There is not an obvious ICI dose threshold for the development of ICI-related sarcoidosis-like reactions. Corticosteroid treatment or other anti-sarcoidosis treatments have not been required for all cases of ICI-related sarcoidosis-like reactions. The most

common factor that led to the initiation of corticosteroid treatment was persistent patients' symptoms, including fatigue, fever and dyspnea. The lung and skin were common organs involved with ICI-related sarcoidosis-like reactions.

Sarcoidosis-like reactions during anti-CTLA-4 treatment most commonly occur in the lung, and typically present with pulmonary nodules and mediastinal lymphadenopathy.[32,33] (Figure 1.) Rarely, co-existent intra-abdominal lymphadenopathy is observed.[34] Ground-glass pulmonary infiltrates are uncommon.[35] Similar to non-drug-induced sarcoidosis, sarcoidosis-like reactions demonstrate fluorodeoxyglucose uptake in involved tissues on positron emission tomography scans.[32] Two retrospective radiographic studies have examined the incidence of thoracic sarcoid-like reactions in patients undergoing anti-CTLA-4 treatment. Bronstein and colleagues reported that 8 out of 119 patients (6.7%) who received anti-CTLA-4 treatment (tremelimumab or ipilimumab) for advanced metastatic melanoma presented clinically silent radiologically benign thoracic lymphadenopathy.[36] These radiologic manifestations were noticed after a median interval time of 6.3 months after treatment was initiated. In a more recent study, 8 out of 147 patients (5%) undergoing ipilimumab treatment for melanoma developed radiologically sarcoid-like lymphadenopathy after a median interval time of 3.2 months from the initiation of therapy.[34] Although as previously mentioned, the presence of mediastinal adenopathy does not secure the diagnosis of a sarcoidosis-like reaction and could represent reactive lymphadenopathy associated with an irAE, 3 out of 8 patients had also concomitant pulmonary

parenchymal findings consistent with sarcoidosis.

The skin is the second most commonly involved organ with anti CTLA-4-induced sarcoidosis-like reactions. Dermatological symptoms often precede the detection of pulmonary infiltrates and lead patients to seek medical care. These skin lesions can range from localized plaques and nodules to generalized cutaneous eruptions.[37,38,33,39] Lofgren syndrome as well as cutaneous granulomatous infiltration of a tattoo has been reported in a patient with metastatic urothelial cancer on combination therapy with a CTLA-4 and a PD1 inhibitor.[40]

Similar to sarcoidosis, the phenotypic expression of sarcoidosis-like reactions can involve organs other than the lung or skin. Such organ involvement is often identified via the restaging of the underlying malignancy with 18F-fluorodeoxyglucose positron emission tomography (FDG/PET). Granulomatous infiltration of the spleen from an ICI-induced sarcoidosis-like reaction can present as splenomegaly with a homogenous uptake of 18FDG[32] or small intrasplenic lesions without splenomegaly.[41] Ipilimumab-related interstitial nephritis may exhibit pathologic appearances consistent with granulomatous nephritis.[42,43] Pituitary granulomas[44] and polyneuropathy[31] have also been reported as a complication of ipilimumab treatment. Elevations of the serum angiotensin converting enzyme level have also been reported with ICI-induced sarcoidosis-like reactions.[40,45]

There are significantly less data regarding the development of sarcoidosis-like reactions with PD-1 and PDL-1 checkpoint inhibitors. Monotherapy with nivolumab, an anti-PD-1 drug, for metastatic melanoma has been associated with bilateral hilar and mediastinal lymphadenopathy and skin involvement in one case[46] and pulmonary infiltrates with facial edema in another.[47] Pulmonary and cutaneous sarcoidosis-like reactions have developed in a patient treated with pembrolizumab, another anti-PD-1 drug, for Hodgkin lymphoma[48] and uterine leiomyosarcoma.[49] In a multicenter phase 1 trial of the PDL-1 inhibitor atezolizumab, a sarcoidosis-like reaction developed in one patient out of 207.[27] In another phase 2 trial of atezolizumab as second-line therapy in advanced urothelial carcinoma, one patient out of 315 developed non-necrotizing granulomatous hepatitis.[50]

There are also reported cases of sarcoid-like reactions in patients receiving multiple checkpoint inhibitors simultaneously or successively as part of their anti-tumor treatment. Cutaneous sarcoidosis has been reported in a female patient with metastatic lung adenocarcinoma receiving Ipilimumab and nivolumab.[51] Another patient treated with pembrolizumab for metastatic melanoma because of disease progression on ipilimumab presented with thoracic and skin sarcoidosis.[52]

The reported incidence of sarcoidosis like reactions appears to be different between the two main classes of ICIs. As mentioned previously, the reported incidence of radiological diagnoses of sarcoidosis-like reactions during anti-CTLA-4 treatment is between 5 and 6.7%.[36,34] This particular irAE is less

common with the use of anti-PD-1/PD-L1 blockades, having been reported in one out of 207 patients (<0.5%) that received anti-PD-L1 regimen BMS-39886[24] and in 2 out of 908 patents (0.2 %) in a French registry of patients treated with anti-PD1 and anti-PD-L1 regimens.[56] This difference in irAE incidence could be possibly be attributed the fact that although anti-PD-1 immune checkpoint inhibitors may cause sarcoidosis-like reactions, down regulation of PD-1 expression on CD4+T cells has been associated with spontaneous resolution of sarcoidosis.[25]

The histopathology from reported cases of ICI-induced sarcoidosis-like reactions are identical to that of sarcoidosis. The biopsies reveal focal infiltration by non-caseating epithelioid and giant cell granulomas. These lesions can coalesce into micro-nodules.[31] No malignant cells or eosinophils have been described, while Grocott's methenamine silver (GMS) and acid-fast bacilli (AFB) stains are negative.

Management of checkpoint inhibitor-induced sarcoidosis-like reactions

To date, no case of a sarcoidosis-like reaction has been reported that was refractory to corticosteroid treatment or discontinuation of checkpoint inhibitors. In a case series of 6 patients who developed checkpoint inhibitor-induced sarcoidosis-like reactions, all of them demonstrated resolution of

lymphadenopathy on lung imaging after checkpoint inhibitor discontinuation in a median interval to resolution of 3.1 months, and only one of them received concomitant corticosteroids.[34]

We believe that if checkpoint inhibitor therapy demonstrates a significant beneficial effect against a cancer but induces a sarcoidosis-like reaction, it may be prudent to continue checkpoint inhibitor therapy and add anti-sarcoidosis therapy. As is the case for sarcoidosis, sarcoidosis-like reactions do not mandate anti-sarcoidosis therapy, especially if the condition is asymptomatic. Danlos and colleagues reviewed 9 case reports of sarcoid-like reactions induced by ipilimumab used to treat melanoma and found that 56% (5/9) were symptomatic and did not require anti-sarcoidosis therapy.[46]
In cases of a sarcoidosis-like reaction where the checkpoint inhibitor therapy has been equivocal or ineffective, discontinuation of chemotherapy could be considered, which should resolve the sarcoidosis-like reaction.

Another reason not to discontinue an checkpoint inhibitor when an irAE, or specifically, a sarcoidosis-like reaction occurs is that it has been postulated that an irAE actually depicts an effective granulomatous anti-melanoma response due to inflammation and cross-reaction with melanoma antigens as a result of anti-CTLA-4 treatment.[31] There is significant clinical evidence supporting an association between anti-CTLA-4 induced irAES and a beneficial anti-tumor response. O'Regan and coworkers reviewed a large number of clinical ipilimumab studies and found that the development of an irAEs was predictive of a better clinical response.[53] Additionally, cohorts of

melanoma patients in ipilimumab trials with high irAE rates were those with the longest overall survivals.[54] In a recent retrospective analysis, cutaneous irAEs were associated with improved survival in melanoma patients treated with nivolumab,[55] In another retrospective study of 119 patients who received anti-CTLA-4 treatment, the 20 patients with radiologic manifestations of immune-related adverse events, including sarcoidosis-like reactions, had a better response compared to the 99 patients without any radiologic manifestations of an irAE: there was a disease control rate of 55% and a 25% complete response rate in the irAE group versus 10% and 3% among the patients who did not develop irAEs.[36]

Conclusion

With the increasing use of checkpoint inhibitors for the treatment of cancers, clinicians should become familiar with associated sarcoidosis-like reactions. A sarcoidosis-like reaction may be misinterpreted on imaging studies as treatment failure and tumor progression, similar to the other immune-mediated adverse events. A biopsy of tissue suspected to be involved should be strongly considered to differentiate immune-mediate adverse events from tumor progression if the latter is a reasonable possibility. At present, it is unknown whether a sarcoid-like reaction of malignancy and sarcoidosis can

be differentiated by clinical tests or biomarkers, including biomarkers associated with sarcoidosis activity. Although sarcoidosis biomarkers have been examined in some of these cases and have been elevated at times, these biomarkers have not been evaluated consistently or rigorously so that definite conclusions can be made about their role in distinguishing sarcoidosis from sarcoidosis-like reactions.

The presence of an ICI-induced sarcoidosis-like reaction does not mandate therapy. Therapy of these reactions is only indicated if they result in significant symptoms or organ dysfunction. These reactions typically respond to corticosteroid therapy. Although ICI may be continued when a sarcoidosis-like reaction develops, these reactions usually resolve if the ICI is discontinued. Further research into the immunologic mechanisms involved in the development of ICI-induced sarcoidosis-like reactions may give insights into the immunopathogenesis of sarcoidosis.

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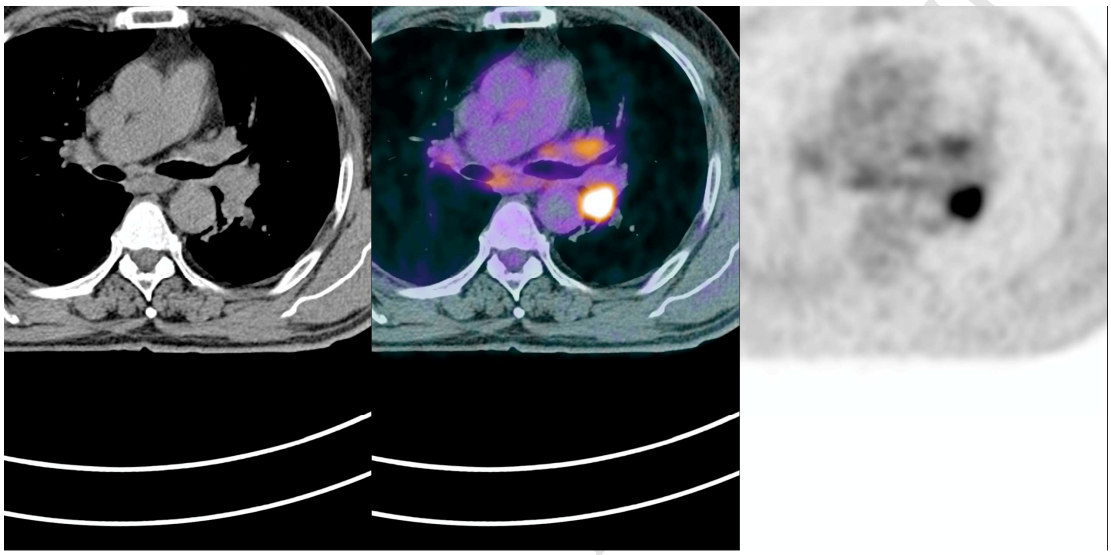
Table 1. Reported ICI-induced sarcoidosis drug reactions (N=23)*

Drug (N, %)	ipilimumab (14, 61%), novolumab (2, 9%), pembrolizumab (2, 9%), ipilimumab plus novolumab or pembrolizumab (4, 17%), unspecified anti-PD-L1 antibody (1, 4%)
Weeks on therapy until drug reaction: (range, median)	3 - 92, 14
Underlying malignancy (N, %)	melanoma (18, 78%), lymphoma (1, 4%), uterine carcinoma (1, 4%), lung carcinoma (1, 4%), uretheral carcinoma (1, 4%), prostate carcinoma (1, 4%)
Organ involved (N, %)†	mediastinal lymph node (15, 65%), skin (11, 48%), lung (10, 43%), extrathoracic lymph node (7, 30%), spleen (4, 17%), neural tissue (2, 9%), eye (1, 4%), bone (1, 4%)
Organ biopsy showing granulomas (N, %)‡	skin (11, 48%), mediastinal lymph node (8, 35%), lung (6, 26%), extrathoracic lymph node (2, 9%), spleen (1, 4%)
Course of action (N, %)	discontinuation of ICI plus corticosteroid therapy (7, 30%), discontinuation of ICI (6, 26%), corticosteroid therapy (5, 22%), no action taken (3, 13%), not specified (2, 9%)
Outcome (N, %)	improvement (11, 48%), resolution (10, 43%), not specified (2, 9%)

ICI: immune checkpoint inhibitor; PD-L1: programmed cell death protein-ligand 1; *: based on references #27, 31-33, 35, 37-41, 44-52, 56-58; †: multiple organs involved in 17/23 (74%) patients, mean number of organs = 51/23 (2.2); ‡: 5 patients had multiple organs biopsied

Legends to the Figures
Figure 1:

67-year-old man received nivolumab for adenocarcinoma of the lung, 3 mg/kg IV, Q2W. Restaging with FDGPET/CT imaging after four doses of nivolumab revealed response at most tumor locations. However, FDGPET/CT imaging also revealed new, metabolically active, enlarged mediastinal and hilar lymph nodes (Figure A).



Endobronchial ultrasound-guided biopsy revealed focal sarcoid like reaction. Notice the non-necrotic confluent granulomas mimicking sarcoidosis, with rare multinucleated giant cells. (Figure B: H-E/ 10X magnification; Figure C: 20X magnification).