Human Pathology (2019) **91**, 69–76

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Human PATHOLOGY

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Original contribution

Immune checkpoint blocker-related sarcoid-like granulomatous inflammation: a rare adverse event detected in lymph node aspiration cytology of patients treated for advanced malignant melanoma☆,☆☆

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Received 24 April 2019; revised 7 June 2019; accepted 1 July 2019

Keywords:
Sarcoid-like granulomatous inflammation;
Fine needle aspiration (FNA);
Melanoma;
Immune checkpoint blocker;
Programmed cell death receptor 1/ programmed cell death ligand 1 (PD-1/PD-L1);
Cytotoxic T lymphocytes–associated antigen 4 (CTLA-4);

Summary Immune checkpoint inhibitors are a major breakthrough in the field of oncology. Targets for approved immune checkpoint inhibitors are cytotoxic T-lymphocytes-associated antigen 4 (CTLA-4) and programmed cell death receptor 1/programmed cell death ligand 1 (PD-1/PD-L1). Five patients (four males and one female) were treated with immune checkpoint inhibitors for advanced melanoma (stage III). None of them had prior history of autoimmune disorders, AIDS, or sarcoidosis. The PET/CT imaging studies showed new onset lymphadenopathy suspicious for malignancy. Four patients had cutaneous melanoma and one had vaginal melanoma. Three patients were treated with single agent (two Nivolumab, one Ipilimumab) and two with double agents (Ipilimumab and Pembrolizumab, or Ipilimumab and Nivolumab). PET/CT showed mediastinal multistational lymphadenopathy in four cases and peri-portal lymphadenopathy in one patient. Ultrasound-guided fine needle aspiration (FNA) biopsy showed numerous sarcoid-like granulomatous inflammation, while the fungal and mycobacterial infections were excluded. Cytomorphologically, the granulomas were numerous, mostly large, cellular and non-necrotizing. Multi-nucleated giant were rare or not seen at all. Cell blocks did not show any fibrosis. Other adverse effects included mouth sores, flu-like symptoms, arthritis, muscle aches, skin rashes,

☆ **Note:** The authors have no financial conflict of interest to disclose.

☆☆ **Authors' contribution: Erika F. Rodriguez:** conceptualization, data curation, formal analysis, investigation, methodology, resources, software, validation, writing - original draft, and writing - review and editing. **Evan Lipson**: conceptualization, data curation, investigation, methodology, resources, contribution to original draft, and writing - review and editing. **Karthik Suresh**: conceptualization, data curation, investigation, methodology, resources, contribution to - original draft, and writing - review and editing. **Laura Capelli**: conceptualization, data curation, investigation, methodology, resources, contribution to - original draft, and writing - review and editing. **Sara E. Monaco:** conceptualization, data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, writing - original draft, and writing - review and editing. **Zahra Maleki:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing - original draft, and writing - review and editing.

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https://doi.org/10.1016/j.humpath.2019.07.001

Lymphadenopathy;
Ipilimumab;
Pembrolizumab;
Nivolumab

mild and severe colitis. The treatment was stopped and patients received prednisone. One patient developed severe adrenal insufficiency, which prolonged prednisone tapering. Their condition improved and lymphadenopathy was resolved in follow-up imaging. Sarcoid-like granulomatous inflammation is an adverse event in patients treated with immune checkpoint therapy such as Ipilimumab and Nivolumab. It can present as enlarged lymph nodes in PET/CT imaging suspicious for malignancy. FNA can serve as a minimally invasive tool to investigate the underlying cause of lymphadenopathy in this subset of patients.

1. Introduction

Immunotherapy with immune checkpoint inhibitors is a major breakthrough in the field of oncology. These drugs block inhibitory molecules to enhance T-cell immune responses against malignant cells.

Targets for approved immune checkpoint inhibitors are cytotoxic T-lymphocytes-associated antigen 4 (CTLA-4) and programmed cell death receptor 1/ programmed cell death ligand 1 (PD-1/PD-L1). CTLA-4 inhibitors such as Ipilimumab are approved by the FDA (Food and Drug Administration) for the treatment of advanced melanoma [1]. In addition, PD-1/PD-L1 inhibitors have been approved by FDA to treat several malignancies including melanoma, non-small cell lung cancer, head and neck malignancies, urothelial cell carcinoma, renal cell carcinoma, uterine cervical cancer, Hodgkin lymphoma, Merkel cell carcinoma, and microsatellite instability-high or mismatch repair deficient tumors [2,3]. Some of the reported immune related adverse effects are fatigue, infusion-related reaction, dermatologic and mucosal such as rush, pruritus and mucositis. Diarrhea/colitis, hepatotoxicity with abnormal liver function test, pneumonitis, and endocrinopathies are also common. Other less common adverse effects are rheumatologic such as arthritis and musculoskeletal [4-6]. Sarcoid-like granulomatous inflammation is a very rare adverse effect that has been reported [2,3,7-11]. The mechanism of immune checkpoint induced sarcoid-like reaction remains unknown. It is hypothesized that it is due to an increase of the total T-cells counts [12,13]. However other authors have postulated that the sarcoid-like immune reaction is secondary to release of interleukin-2 and interferon gamma [14]. Moreover, the development of pulmonary sarcoid-like granulomas is also reported in association with vaccine therapy in a patient with advanced melanoma [15].

Small biopsies and cytology specimens have been utilized to evaluate PD-L1 expression in specimens with lung cancer, particularly non-small cell carcinomas, in an effort to determine treatment options [16,17] [18]. In addition, given the dramatic increase in cancer patients receiving immunotherapy for various malignancies [10], understanding the potential adverse reactions associated with these therapies is important for pathologists evaluating small biopsies in these cancer patients. Upon follow-up, patients may develop new imaging findings or symptoms that could be attributed to recurrent/metastatic disease or reactive and inflammatory changes associated with treatment effect. From the patient management standpoint, it is of paramount importance to evaluate the enlarged lymph nodes through FNA or a small biopsy in order to exclude a metastatic process, and to identify the etiology of the lymphadenopathy. The pathologic diagnosis of the enlarged lymph nodes may potentially alter the treatment regimen for the patient. Herein, we report five patients treated with anti-PD-1/PD-L1 and/or anti-CTLA-4 who presented with mediastinal/hilar and peri-portal lymphadenopathy clinically suspicious for malignancy.

2. Materials and methods

2.1. Cytology collection, sample preparation

An endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) was performed on four out of five cases (1, 2, 4 and 5) to further investigate the newly developed mediastinal lymph adenopathy. An average of eight passes were performed on all EBUS guided FNA cases. An upper endoscopic ultrasound guided FNA of periportal lymph node was performed to assess the periportal lymphadenopathy. Specimen adequacy was evaluated with rapid on site evaluation (ROSE) by an experienced cytotechnologist. The aspirates were smeared on glass slides and either air-dried or fixed in 95% ethanol and stained with Diff-Quik and/or Papanicolaou stain, respectively. Needles were rinsed with Hanks' balanced salt solution and the material made into paraffin cellblocks, and 4-μm sections were stained with hematoxylin and eosin. Cellblocks were available on all cases.

2.2. Clinical history

2.2.1. Case 1

The first patient is a 32-year-old white woman with a history of malignant melanoma (histologic type: not otherwise specified; Breslow thickness: 4.25 mm; ulceration: present; mitoses/ 5 mm [2]; regression: absent; and tumor

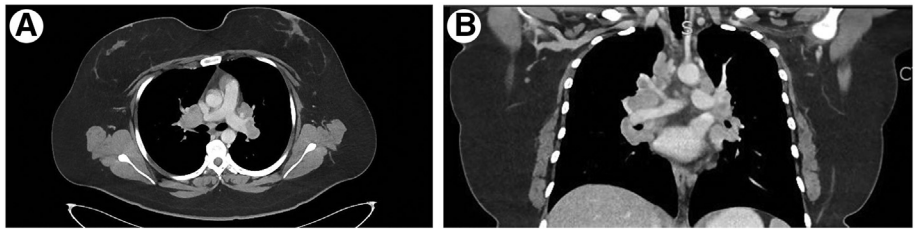

Fig. 1 A and B, Chest CT of case 1 shows new onset hilar and mediastinal lymphadenopathy.

infiltrating lymphocytes: present; focally brisk) of the left upper shoulder status post wide local excision and sentinel lymph node excision with focal involvement of the left axillary sentinel lymph node with metastatic melanoma, Stage III C receiving adjuvant therapy with Nivolumab 480 mg IV, two doses (anti-PD-1 antibody). The diagnosis of melanoma was confirmed with positive staining for SOX10 and HMB45. The patient was T4b, N1a, Mx, Stage IIIC (AJCC version 8). Per National Comprehensive Cancer Network (NCCN) guidelines, it was recommended that she follow-up with medical oncology every 4–6 months for 5 years, then annually thereafter. This included regular imaging to screen for recurrence or metastatic disease (first 5 years only). Two months after excision, she received 4 cycles of adjuvant SCOM07 Nivolumab, each cycle included 480 mg SCOM07 Nivolumab every 4 weeks. She experienced sores in her mouth, mainly her upper gum after her receiving the first cycle of Nivolumab, which was resolved gradually. However, the patient developed musculoskeletal symptoms after her third infusion of Nivolumab. She felt flu-like symptoms, soreness in her muscles, and stiffness in joints initially in the wrists, knees and ankles. She had no previous history of autoimmune disease or skeletal muscle symptoms and no family history of connective tissue disease. A thorough evaluation for autoantibodies was performed and all the tests (PL-7, PL12, MI-2, Ku, EJ, OJ, SRP, JO-1, Scleroderma IgG, Cardiolipin, Ab, IgG, IgM, IgA. B2 Glycoprotein IgG, B2 Glycoprotein IgGM, B2 Glycoprotein IgGA, Rheumatoid Factor, Cyclic Citrullinated Peptide 3 IgG, Ro52 IgG, Ro60 IgG, La IgG, RNP IgG, Smith (Sm) IgG, DNA Antibody Screen, Nuclear Antibody Screen, Serum (ANA), T-Spot TB Test) were negative. An elevated C-reactive protein was the only positive finding. On physical exam, she had multiple and bilateral swollen and tender joints. She was diagnosed with immune checkpoint-inhibitor-induced inflammatory arthritis treated with NSAIDS (Naproxen 500 mg twice a day) with improvement of her symptoms. She shortly thereafter developed mild cough and dyspnea. CT scan of chest/abdomen and pelvis revealed new mediastinal and bilateral hilar lymphadenopathy raising the differential of metastatic disease, sequelae of patient's immunotherapy, sarcoidosis, lymphoma, or infection (Fig. 1B). An endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed on stations 4R, 7, and 11R. The microscopic examination of aspirated lymph nodes revealed granulomatous inflammation. Her immunotherapy stopped and Prednisone 40 mg daily was started and was tapered off 5 weeks after. However, 3 months after, Prednisone 20 mg daily was restarted because of recurrence of her symptoms (wheezing, shortness of breath). The patient's symptoms gradually improved and Prednisone was tapered off 12 weeks after. Her last CT scan of the chest revealed resolution of the previously noted mediastinal and hilar lymphadenopathy (Table 1).

2.2.2. Case 2

The patient is a 31-year-old white man with history of Stage IIIC melanoma. His initial diagnosis of left scalp melanoma (histologic type: superficial spreading; Breslow thickness: at least 2.3 mm; ulceration: present; mitoses/3 mm [2]; regression: absent; and tumor infiltrating lymphocytes: absent) was done 4 years prior. He subsequently underwent wide excision of the scalp skin for melanoma and excision of the left four sentinel lymph nodes. The excised scalp tissue showed residual invasive and in-situ melanoma. The depth of invasion was 0.9 mm. There was no evidence of lymphovascular invasion, perineural invasion, or microsatellitosis. Three out of four left sentinel lymph nodes were involved with metastatic melanoma. Melan A and HMB45 immunostains confirmed the diagnosis. A CT scan of the chest, abdomen and pelvis was performed before his initial surgery and there was no evidence of mediastinal, abdominal or pelvic lymph adenopathy. A melanoma mutation molecular study panel including *BRAF, KIT, NRAS, and PIK3CA* was done and the tumor was *BRAF*- V600E mutated. The patient received two doses of Ipilimumab, 3 mg/kg 6doses (anti-CTLA-4 antibody). However, prior to starting the third dose, he developed a neck mass only 3 weeks after the excisional surgery and left neck lymph node excisions. He underwent the second excision including left parotidectomy and lymph node dissection. Histologic examination showed metastatic melanoma to one of six intraparotid lymph nodes, and 2 out of 50 neck lymph nodes. The parotid tissue was unremarkable. Therefore, his third dose was canceled. He had his third neck lymph node dissection due to enlarged lymph nodes 10 months after his second surgery. Two out of 30 left neck lymph nodes were positive for metastatic melanoma. CT scan of the chest, abdomen and pelvis was performed

Table 1 Patients' demographic, site of primary malignant melanoma, immunotherapy, imaging findings, and other adverse effects related to therapy

	Patient demographics Age (y), gender	Site, stage of malignant melanoma	Immune checkpoint inhibitors, dose	Time interval between immunoetherapy and granuloma detection (mo)	Imaging findings after Immune checkpoint Inhibitor therapy	Other adverse effects after immune checkpoint inhibitor therapy	Follow-up
1	32, male	Upper shoulder, Stage IIIC	Nivolumab, 480 mg (flat dose) IV q4weeks, 4 cycles	44	Mediastinal and hilar lymphadenopathy	Mouth sores, flu-like symptoms, arthritis, muscle aches	Stable, no evidence of metastatic disease
2	31, male	Left scalp, stage III	Ipilimumab 3 mg/kg q3weeks × 4 doses, then two additional doses 12 weeks apart	43	Multi-station mediastinal and hilar lymphadenopathy	None	Stable, no evidence of metastatic disease
3	71, male	Right face, stage III	Nivolumab, 480 mg (flat dose) IV q4weeks 3 cycles	5	Periportal lymphadenopathy	Skin rashes, loose stools	Stable, no evidence of metastatic disease
4	61, male	Right upper extremity, stage III	Pembrolizumab, 200 mg IV every 3 weeks and CMP-001 intratumoral dose escalation (1 mg, 3 mg, 5 mg, 7.5 mg, and 10 mg)	24	Bilateral hilar and mediastinal lymphadenopathy	Mild colitis	Stable, no evidence of metastatic disease
5	64, female	Vagina, stage III	Ipilimumab 3 mg/kg plus Nivolumab 1 mg/kg × 3 cycles followed by Nivolumab 240 mg IV ×1.	9	bilateral hilar and mediastinal lymphadenopathy	Severe colitis, dermatitis	Stable, no evidence of metastatic disease

Abbreviations: IV, intravenous; q, every.

3 years after his immunotherapy and showed multiple new, multi-station mediastinal and hilar lymphadenopathy measuring up to 4.0 cm, which was highly suspicious for metastatic melanoma. EBUS-guided FNA was performed and all three aspirated lymph nodes showed non-necrotizing granulomatous inflammation and no evidence of metastatic melanoma. He did not receive any prednisone for his lymph adenopathy. His last CT of chest, abdomen and pelvis showed significant interval improvement in mediastinal and hilar lymphadenopathy, which were subcentimeter in size.

2.2.3. Case 3

The patient is a 71-year-old Caucasian male with a history of stage III malignant melanoma of the right face (histologic type: superficial spreading; Breslow thickness: at least 1.4 mm; ulceration: present; mitoses/ 9 mm [2], regression: absent, and tumor infiltrating lymphocytes: present, non-brisk) status post wide resection and excision of three negative lymph nodes. Subsequent right neck lymph node dissection revealed one out of 39 lymph nodes involved with metastatic melanoma. The metastatic tumor measured 3.4 cm with 1.5 mm extranodal expansion. The diagnosis was confirmed with SOX10, and Melan-A immunostains. NGS solid tumor panel was performed. The tumor cells showed *PTEN* (p.P213L) and *TP53* (p.P278F) mutations. The patient completed 3 cycles of SCOM07a, Nivolumab 480 mg (flat dose) infusion every 4 weeks. He developed skin rashes and loose stools. A PET/CT imaging study was performed 3 months after his immunotherapy, which was unremarkable except a hypermetabolic porta hepatis lymph node measuring 1.3 × 1.5 cm (table position 1423.1) with SUV max 3.6, increased in size compared to prior CTs, suspicious for nodal metastatic involvement. An upper endoscopic ultrasound-guided (EUS) FNA of periportal lymph node was performed, which showed granulomatous inflammation. GMS and AFB stains were negative for fungal and mycobacterial microorganisms, respectively. The patient was treated with Prednisone 20 mg oral daily. His condition improved and prednisone tapered over 4 weeks.

2.2.4. Case 4

The patient is a 61-year-old Caucasian man with a history of melanoma of the right upper extremity (stage IIIB, T4b N1a M0), status post wide local excision, sentinel lymph node biopsy, and completion lymph node dissection. Patient was then treated with Pembrolizumab, and developed in transit metastases while on therapy, which were excised. The patient was then started on Ipilimumab and Pembrolizumab (Pembrolizumab dose: 200 mg IV over 30 minutes every 3 weeks and CMP-001 intratumoral dose escalation (1 mg, 3 mg, 5 mg, 7.5 mg, and 10 mg). He developed grade 2 colitis and diarrhea 9 months after starting immunotherapy. He was treated with Prednisone, 1 mg/kg (81 kg, 80 mg, tapered to 10 mg dose) and responded well.

Two years after the initial melanoma diagnosis, the patient had restaging with PET/CT scan, which revealed bilateral hilar and mediastinal lymphadenopathy, which was FDG avid (SUV ranging from 4.09–7.37), and no lung masses. Thus, EBUS-TBNA was performed to determine if the mediastinal and hilar lymphadenopathy was due to metastatic melanoma, and rapid on-site evaluation was negative for malignant cells with granulomas identified. EBUS-TBNA of the right paratracheal, subcarinal, and right hilar lymph nodes revealed non-necrotizing granulomas with no morphologic or immunophenotypic evidence of metastatic melanoma. Based on the EBUS-TBNA findings, the immunotherapy was discontinued, and the patient's lymphadenopathy subsided on the CT-scan done 4 months after the EBUS-TBNA.

2.2.5. Case 5

The patient is a 64-year-old Caucasian female with history of vaginal melanoma (superficial spreading, 4.5 × 2.5 × 1.5 cm) status post wide local excision/vulvectomy and sentinel lymph node biopsy, which was negative for malignancy. The tumor demonstrated no molecular alterations including BRAF. She completed 3 of 4 cycles of combined Ipilimumab 3 mg/kg plus Nivolumab 1 mg/kg, followed by one cycle of Nivolumab 240 mg infusion. However, her immunotherapy was complicated by developing grade III dermatitis and grade III autoimmune colitis. The autoimmune colitis was refractory to steroids, and prolonged steroid taper led to prolonged adrenal insufficiency, and multiple admissions. The patient's PET scan 5 months after immunotherapy showed mediastinal lymphadenopathy. The next PET/CT follow up was performed 3 months after showing worsening mediastinal, intrathoracic and upper abdominal lymphadenopathy. An EBUS-guided FNA was performed on lymph nodes stations 4R, 10 L, and 11R. The microscopic assessment of the aspirated material showed granulomatous inflammation. In her last visit, she denied shortness of breath, chest pain, cough, fatigue, nausea, vomiting, diarrhea, or skin rashes (Table 1). She was treated with Prednisone, 80 mg daily, which was tapered over 21 days.

3. Cytomorphologic findings

Microscopic examination of aspirated material revealed numerous non-necrotizing granulomatous inflammation in all lymph nodes in all five cases (Fig. 2F). The granulomas were variable in size, mostly large. The epithelioid histiocytes contained abundant cytoplasm and focally surrounded by pockets of mature small lymphocytes in the cellblocks. The clusters of epithelioid histiocytes were quite cellular with a peripheral cuff of crushed small lymphocytes on the smears. In contrast to granulomas in sarcoidosis, the granulomas associated with immunotherapy were not associated with hyalinized fibrosis, leading to quite cellular aspirated. In addition, there were only rare or no multinucleated giant cells scattered throughout the smears. The cytology samples from patients one and four were also submitted to flow

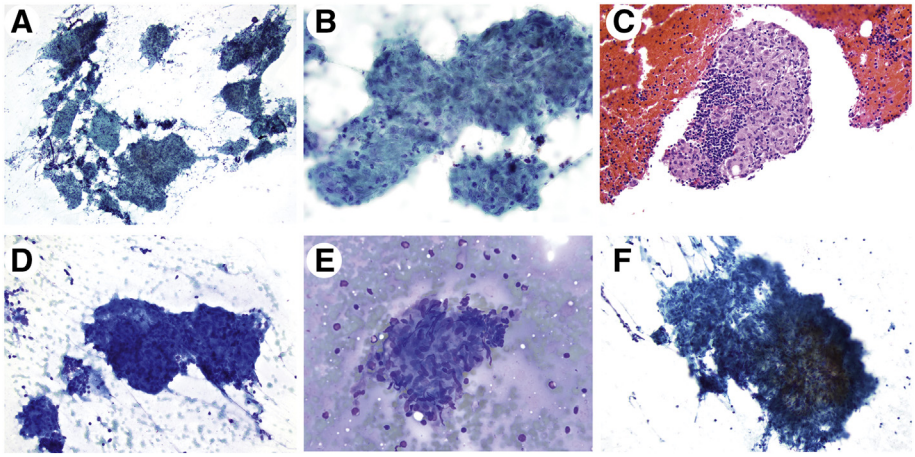

Fig. 2 A, Case 1, EBUS guided FNA shows numerous granulomas, mostly large in size (original magnification ×40, Papanicolaou stain). B, Case 2, a large granuloma is shown here containing epithelioid histiocytes with abundant cytoplasm and coated with mature small lymphocytes (original magnification ×40, Papanicolaou stain). C, Case 2, a cell block preparation shows a granuloma partially surrounded by pockets of small lymphocytes. There is no evidence of necrosis or malignant cells (original magnification ×20, H&E stain). D, Case 3, aspirated material shows a couple of granulomas composed of numerous epithelioid histiocytes and scattered lymphocytes in the background (original magnification ×40, Diff-Quik stain). E, Case 4, aspirated material shows a granuloma composed of numerous epithelioid histiocytes and scattered lymphocytes in the background (original magnification ×40, Diff-Quik stain). F, Case 5, a very large granuloma is shown here containing numerous epithelioid histiocytes with abundant cytoplasm and mature small lymphocytes (original magnification ×40, Papanicolaou stain).

cytometry studies, which were negative for a lymphoproliferative disorder. GMS and AFB were performed on the cell blocks of all cases and were negative for fungal and mycobacterial microorganisms, respectively. All examined lymph nodes were negative for metastatic melanoma (Table 2).

4. Discussion

We report five cases of patients with advanced metastatic melanoma treated with checkpoint inhibitor immunotherapy that developed lymphadenopathy detected by PET/CT imaging studies, which were suspicious for metastatic melanoma. The mediastinal/hilar lymphadenopathy were evaluated by EBUS-TBNA and the periportal lymphadenopathy evaluated by EUS-FNA and ROSE. The findings in these cases demonstrated non-necrotizing granulomatous inflammation in all biopsied lymph nodes, without any evidence of metastatic melanoma and with no evidence of a fungal or mycobacterial infectious etiology. None of the patients had a history of sarcoidosis or autoimmune disorders. Based on these findings, the patients were followed clinically, and the changes were attributed to the sarcoid-like granulomatous inflammation that has been described in patients treated with immunotherapy [11,19]. The time interval between initiating immune checkpoint inhibitor therapy and lymph adenopathy was 5–44 weeks (mean = 25 weeks), which is in accordance with reported cases [11]. The lymphadenopathy was resolved by discontinuing immunotherapy alone and or with prednisone, treatment for sarcoidosis. All five patients are in stable condition without any evidence of metastatic disease.

Granulomatous inflammation has been described in the lymph nodes of patients undergoing immunotherapy, particularly in melanoma patients compared with other types of malignancies [11,20-24]. Lainez reported a case of sarcoid-like reaction diagnosed on EBUS-TABNA in a patient treated with checkpoint inhibitors for NSCLC [19].The fact that the majority

Table 2 The cytomorphologic features of granulomas in sarcoidosis and sarcoid-like reaction induced by immunotherapy

Cytological finding	Sarcoid	Sarcoid-like reaction with immunotherapy
Overall cellularity	Variable depending on amount of hyalinizing fibrosis	Cellular, given lack of hyalinizing fibrosis
Granulomas	Discrete clusters of epithelioid histiocytes of low to intermediate cellularity and scattered mature small lymphocytes	Cellular and numerous granulomas mostly very large, coated with mature small lymphocytes with a peripheral cuff of crushed lymphocytes, or pockets of small lymphocytes
Multinucleated giant cells	Variable, but typically less than infectious type granulomas	Rare or none
Background	Clean, no necrosis	Clean, no necrosis

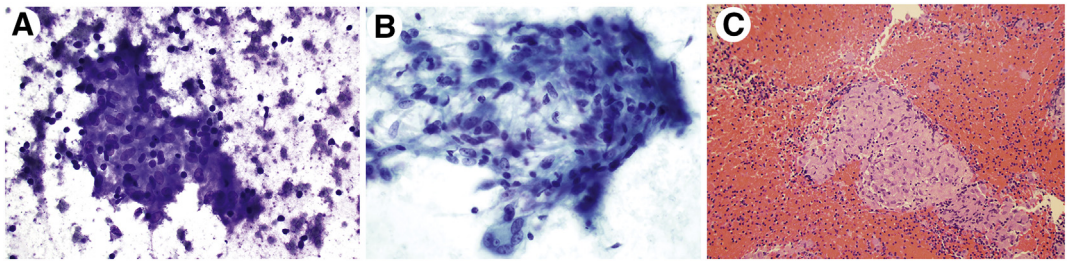

Fig. 3 Non-necrotizing granuloma in sarcoidosis. A, Granuloma is seen comprised of epithelioid histyocytes and scattered mature small lymphocytes (original magnification ×40, Diff-Quik stain). B, A multinucleated giant cell is seen at the edge of the granuloma (original magnification ×40, Papanicolaou stain). C, A cell block shows a non-necrotizing granuloma (original magnification ×20, H&E stain).

of the reports of immune-related sarcoid has been in melanoma patients may reflect the fact that these therapies were first approved and utilized in melanoma patients.

The diagnosis of immune-related sarcoid reaction can be a diagnostic challenge, particularly in patients with melanoma, given the fact that the tumor cells can resemble benign/reactive changes, and granulomatous inflammation can mimic tumors [25]. For example, the spindled nuclei of spindle cell melanoma may morphologically resemble the ovoid nuclei seen in granulomas. Furthermore, melanoma with small cell features could potentially resemble the background small lymphocytes and be challenging to recognize or be misinterpreted as an atypical lymphoid population, prompting material to be sent for flow cytometry and potentially limiting material available for morphological evaluation. Thus, the recognition of the association of sarcoid-like granulomatous inflammation is critical for cytopathologists who evaluate EBUS-TBNAs or EUS-FNAs and communicate with the treating clinicians. This rare case series also illustrates some unique morphological associations with immune-related sarcoid-type reactions that may distinguish them from the non-necrotizing granulomas seen in true sarcoidosis. One such feature is the lack of hyalinized fibrosis and sclerosis, which may be due to the fact that the lymphadenopathy is seen in earlier stages in these cancer patients being followed up regularly with PET/CT imaging and less likely to be a chronic process as seen in true sarcoidosis. This may explain why the EBUS-TBNA or EUS-FNA aspirates are cellular and granulomas are easy to identify. The hyalinized granulomas seen with long-standing sarcoidosis have been associated with unsatisfactory or suboptimal EBUS-TBNA specimens, which can lower the diagnostic yield of EBUS-TBNA in these cases [26]. Furthermore, the granulomas seen in these sarcoid-like reactions in cancer patients on immunotherapy tended to be numerous, with variable sizes, mostly large, very cellular with no or rare multinucleated giant cells (Table 2). At least 2 of the cases were also known to be on combination immunotherapy, which has also been a factor associated with immune-related sarcoid [23]. Similar to true sarcoidosis (Figs. 3C), our cases showed multistation involvement and had an absence of necrosis.

Tirumani et al reported on the radiographic profiling of immune-related adverse events in patients treated with Ipilimumab with sarcoid-like reactions that had only lymph node enlargement similar to our case [6]. Nishino et al [27] reported imaging studies of the lung on patients with sarcoid-like granulomatosis of the lung who usually present with focal areas of consolidation in the lung parenchyma that are frequently associated with a round or nodular surrounding halo of ground glass opacities. Interestingly, our patients did not have any lung lesions. The case with periportal lymphadenopathy is the first reported case of abdominal sarcoid-like graolumatous lymphadenopathy.

Although sarcoid-like reactions have been described in the literature, most of the cases are rare case reports limited to radiologic or histological evaluation, with only rare reports of this entity in the cytology literature. Since EBUS-TBNA is a method of choice to evaluate mediastinal and hilar lymphadenopathy, it is crucial that pathologists be aware of this unusual but significant immunoreaction in patients treated with checkpoint inhibitors. Moreover, awareness of this rare adverse event by clinicians and pathologists would improve patient care and help them have a better understanding of treatment with checkpoint inhibitors.

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