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CASE REPORT

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A Peritoneal Granulomatous Lesion with Dense Histiocytic Infiltration Due to Nivolumab Treatment

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ABSTRACT In the current practice of oncology, immunological treatments have an expanded spectrum owing to increased efficacy in various indications for the same tumor and the rising number of responsive cancers, by the novel agent development. In this report, the emergence of a peritoneal lesion is presented in a 50-year-old male patient under nivolumab treatment for lung adenocarcinoma. Granulomatous tissue with dense histiocytic infiltration and necrotic foci was revealed on histopathological examination. Immune-related granulomatous lesions are commonly defined as sarcoid-like and no necrosis, generally located in the mediastinal lymph nodes, lungs, and skin. To the best of our knowledge, this is the first report of an immune-related granulomatous lesion with histiocytic infiltration and necrotic foci, located on the peritoneum. The etiopathogenesis and clinicopathological features of immunotherapy-related granulomatous lesions and their potential predictive role on anticancer efficacy should be better understood.

Keywords: Immunotherapy; nivolumab; adverse effects; granulomata

The term "immune checkpoint inhibitor (ICPI)" or immunotherapy, includes many agents in the form of monoclonal antibodies. Ipilumumab, atezolizumab, and nivolumab are examples of these agents targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death ligand-1 (PDL-1), and programmed cell death protein 1 (PD-1), respectively; thus, affecting the intracellular signal pathways and regulate impaired immune response as an important component of tumoral escape mechanisms. Many ICPI agents capable of promoting permanent anti-tumor immune response have been introduced in the oncology practice. Both the therapeutic era of ICPI agents for the indicated tumors (used as adjuvant treatments after metastatic efficiency) and their spectrum of efficacy on many cancer types (nivolumab indicated for lung cancers following melanomas) are extending continuously.[1,2]

In patients with cancer, immunity-associated side effects can be observed after ICPI treatments, most commonly in the lung, skin, and gastrointestinal system; organs with diffuse lymphocyte infiltration.[3] Many immune-related adverse events such as autoimmune colitis, pneumonitis, hepatitis, endocrinopathies, and cutaneous rashes have been defined.[4] Skin lesions like maculopapular rash, vitiligo, and lichenoid reactions with itching and mucosal toxicity are most commonly observed and appear in 34-39% of cases under anti-PD-1 treatments. Immune-related granulomatous tissue reactions such as granuloma annulare, sarcoidosis with multiorgan involvement, and granulomatous panniculitis have also been reported in parallel to the increasing use of ICPI. Some adverse effects complicate clinical approaches by imitating cancer recurrences or metastases.[5]

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This report presents an ICPI-associated peritoneal dense histiocytic granulomatous tissue lesion in a patient under nivolumab treatment for non-small cell lung cancer. To the best of our knowledge, this case may be interesting and unique in the medical literature, with regard to both its presentation in the peritoneum and nature of the lesion that contained necrosis.

CASE REPORT

A 50-year-old male patient was admitted with progressively increasing chest pain and shortness of breath; a mass was detected in the left lung using a radiograph and positron emission tomography with computed tomography (PET-CT) (Figure 1). He was a non-smoker. After performing staging tests and transthoracic biopsy, T3N2M0 lung adenocarcinoma was diagnosed. Four cycles of cisplatin-docetaxel were planned for neoadjuvant chemotherapy. However, after the first four cycles of chemotherapy, the disease progressed. Therefore, the patient was accepted as inoperable. The tissue specimen mutation analyses and PDL-1 tests were performed. The next-generation sequencing analysis was negative for epidermal growth factor receptor, anaplastic lymphoma kinase (ALK), and reactive oxygen species (ROS)-1 mutations. In addition, fluorescence in situ hybridization testing was performed to confirm the results for ALK and ROS mutations. The Dako method was used to obtain PDL-1 positivity (95%). Immunotherapy with nivolumab 3 mg/kg every 2 weeks was initiated. The patient's symptoms (shortness of breath and chest pain) clinically regressed after the sixth week of the treatment. At the end of 3 months, the achievement of a complete response was confirmed using PET-CT (Figure 2). In the 20th month of the treatment, PET-CT demonstrated a 1.6×1.5 cm mass detected in the peritoneum adjacent to the liver using 18F-fluorodeoxyglucose maximum standardized uptake value of 9.6 (Figure 3).

The peritoneal lesion was completely excised surgically, and the histopathological examination revealed granulomatous tissue with dense histiocytic infiltration and necrotic foci (Figure 4). Ziehl-Neelsen and periodic acid-Schiff stains were negative. The patient had no history of autoimmune diseases. The lesion was diagnosed as an immune-related side effect based on the clinical, radiologi-

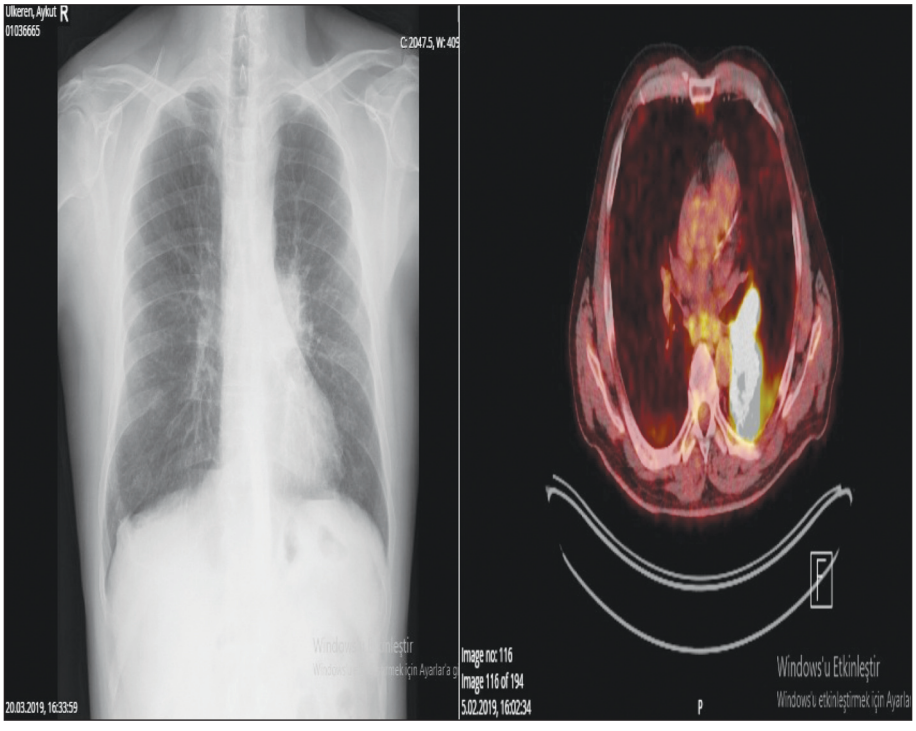

FIGURE 1: Mass in the left lung on radiograph and positron emission tomography with computed tomography at the time of diagnosis.

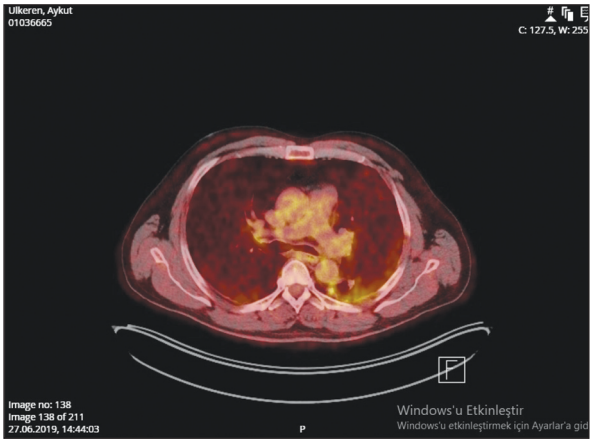

FIGURE 2: Positron emission tomography with computed tomography image after 3 months of treatment.

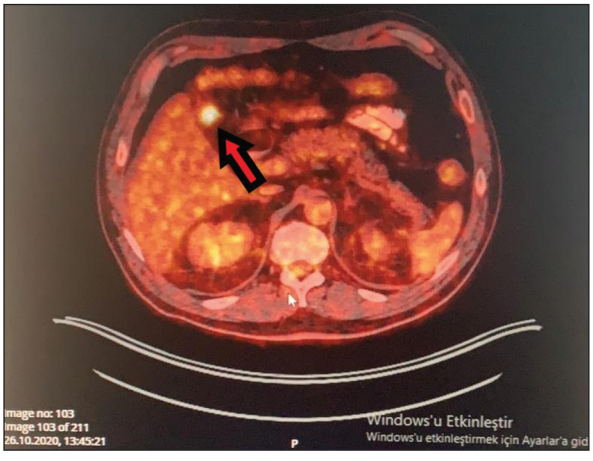

FIGURE 3: Mass lesion in the peritoneum adjacent to the liver in positron emission tomography/computed tomography.

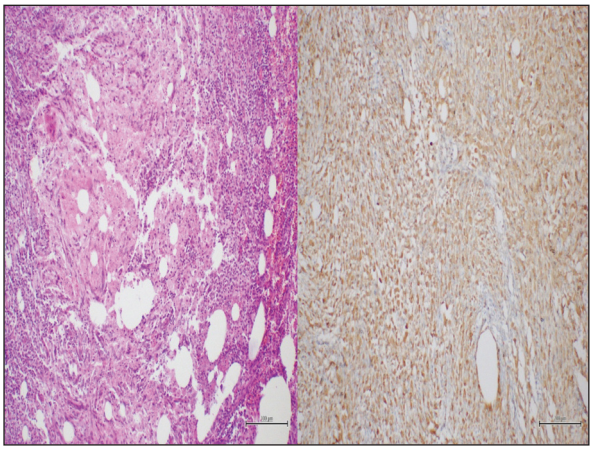

FIGURE 4: A) Focal areas of necrosis and accumulation of histiocytes (H&E, 10X); B) CD68 spindle positive staining in histiocytes (H&E, 10X).

cal, and histopathological findings. The patient is currently in the 23rd month of nivolumab treatment with a complete response and no additional toxicity.

The Naranjo adverse drug reaction probability scale was used to evaluate the likelihood that the peritoneal granulomatous lesion was due to the use of nivolumab, yielding a total score of 6 (possible) (Table 1).

The informed consent form was obtained from the patient in the case.

DISCUSSION

Nivolumab is a purely human immunoglobulin G4 anti-PD-1 ICPI antibody, selectively blocking the interaction between PD-1 and its ligands PD-L1 and PD-L2. This agent blocks the negative signalization pathway that inhibits T-cell activation and proliferation. ICPIs used in oncology practice also interfere with the equilibrium between cytotoxic T and Th1/Th17 and regulatory T cells in cancer tissues. PD-1/PD-L1 blockade has been associated with Th17 cell hyperactivity and increased interleukin 17 expression. As a result of the imbalance between T helper cells and co-stimulatory molecules, these agents are thought to play a role in the pathogenesis of granulomatous lesions.[6-8] PD-1/PD-L1 signaling blockade causes increased expressions of phosphatidylinositol 3-kinase in the mechanistic target of the rapamycin (mTOR) pathway. Structural activation of the mTOR complex 1 pathway is shown to induce spontaneous granuloma formation in macrophages.[9-11] Thus, the interaction blockade between PD-1/PD-L1 by ICPIs may promote granuloma formation by chronic activation of the mTOR pathway.

ICPIs related to sarcoid-like granulomatous lesions have also been reported. In the immunopathogenesis of these lesions possibly causing both hypoactive or hyperactive immune responses, monocyte-derived histiocytes and CD4(+) Th1 cells are presumed. Consequently, increased T cell proliferation by PD-1 signaling inhibition may cause a hyperactive immune response.[12,13]

Seve et al. were among the pioneers to describe sarcoidosis-like granulomatous tissue lesions owing to immunological treatments in seven patients with melanoma.[14] Among these, the lesions appeared after

TABLE 1: Naranjo adverse drug reaction probability scale

Naranjo Adverse Drug Reaction Probability Scale				
Question	**Yes**	**No**	**Do not know**	**Score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total score			**6**

interferon and CTLA-4 inhibitor ipilimumab therapies in 6 and 1 patient, respectively. Although it has been more frequently reported in patients with melanoma since then, granulomatous tissue reactions have also been reported in those under nivolumab, pembrolizumab, and ipilimumab treatments for various cancers.[12,15,16] A subset of patients developing granulomatous-like lesions during ICPI therapy, appear to have a favorable therapeutic response.[17] Although it was speculated that granulomatous lesions might predict a response to immunological cancer treatments, the number of reported cases was insufficient for a conclusion. The proposal that steroid treatment for the management of immune-related adverse events might decrease the efficacy of immunotherapy is also controversial in the light of previous articles.[18,19]

Cancer treatment-related granulomatous lesions are not specific to ICPI treatments. It has been defined previously in other patients under methotrexate, alpha interferon, cisplatin, interleukin 2, and vemurafenib treatments for solid or hematological malignancies.[20] Furthermore, infectious causes of granulomatous lesions should be excluded by special stains and/or tissue cultures.

In the current medical literature, immune-related granulomatous lesions have been mostly defined as sarcoid-like and have no necrosis. In the presented case, the granulomatous lesion had dense histiocytic infiltration and necrotic foci. To the best of our knowledge, this is the first report of an immune-related granulomatous tissue with these features. Additionally, previously reported cases were generally located in the mediastinal lymph nodes, lungs, and skin, and peritoneal localization was not defined previously. With these features, the presented case may be the first in the medical literature.

Although granulomatous lesions owing to immunological treatments are rare, they can emerge at any time during the treatment. These lesions can clinically and radiologically imitate cancer progression and metastasis and interfere with clinical decisions. It is important to recognize and manage these lesions accurately for immunological treatments. The etiopathogenesis and clinicopathological features of immunotherapy-related granulomatous reactions as well as their potential predictive role on anticancer efficacy should be better understood.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the

potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Bilgin Demir;* ***Design:*** *Bilgin Demir, Ali Aytaç;* ***Control/Supervision:*** *Sabri Barutca;* ***Data Collection and/or Processing:*** *İbrahim Meteoğlu, Bilgin Demir;* ***Analysis and/or Interpretation:*** *Bilgin Demir, Ali Aytaç, Sabri Barutca, İbrahim Meteoğlu;* ***Literature Review:*** *Bilgin Demir, Ali Aytaç;* ***Writing the Article:*** *Bilgin Demir, Ali Aytaç;* ***Critical Review:*** *Sabri Barutca;* ***References and Fundings:*** *Bilgin Demir, Ali Aytaç;* ***Materials:*** *İbrahim Meteoğlu, Bilgin Demir.*

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