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Immune checkpoint inhibitor-associated sarcoidosis reaction

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ABSTRACT

Immune checkpoint inhibitors (ICIs) constitute a class of drugs that stimulate the immune system to fight cancer cells. However, they can also induce immune-related adverse events (irAEs) in various organs, including the kidneys. One of the infrequent irAEs associated with ICIs is sarcoidosis, an inflammatory disease that can impact multiple organs, such as the lungs, skin, and lymph nodes. Sarcoidosis is characterized by the formation of granulomas, clusters of immune cells that can potentially harm tissues. In some cases, ICIs can trigger kidney sarcoidosis, leading to impaired renal function. The mechanism through which ICIs initiate sarcoidosis is believed to involve activating T cells and cytokines that foster inflammation.

Hypothesis

Implication for health policy/practice/research/medical education:
The renal sarcoidosis-like reaction is a rare immune-related adverse event (irAE) associated with programmed cell death protein 1 (PD-1) inhibitors, immunotherapy drugs utilized to treat various cancers. PD-1 inhibitors block the PD-1 receptor on T cells, enabling them to attack cancer cells more effectively. However, this mechanism triggers the activation of the immune system, leading to inflammation in various organs, including the kidneys.

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Introduction

Immune checkpoint inhibitors (ICIs) represent a form of cancer immunotherapy whose mechanism blocks specific proteins in immune cells, enabling them to identify and target cancer cells (1) more effectively. While ICIs have demonstrated significant potential in treating various types of cancer, they also have the potential to give rise to immune-related adverse events (irAEs) affecting different organs, including the kidneys (2).

Sarcoidosis is a systemic inflammatory disease characterized by forming granulomas, clusters of immune cells (3). This condition can affect multiple organs, including the lungs, skin, eyes, and kidneys. In ICI therapy, sarcoidosis can develop as an irAE due to immune system dysregulation (4).

Kidney involvement in ICI-associated sarcoidosis is relatively uncommon but has been documented in several case studies. ICIs might trigger an exaggerated immune response, leading to the development of sarcoidosis-like granulomas in the kidney (4).

The renal sarcoidosis-like reaction is characterized by the development of granulomas in the kidneys, which are clusters of immune cells that form in response to inflammation. These granulomas can cause kidney dysfunction and lead to untreated renal failure. Granulomas are small collections of immune cells, primarily macrophages and lymphocytes, that develop in response to the presence of foreign substances or persistent immune stimulation (5,6). Risk factors, such as the type of ICI, treatment duration, and prior history

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of sarcoidosis, may impact the likelihood of developing kidney involvement (4,7). The clinical manifestations of kidney involvement in ICI-associated sarcoidosis reaction can vary from asymptomatic renal abnormalities to overt kidney dysfunction. Common findings include proteinuria, hematuria, and a decline in renal function. Symptoms of a renal sarcoidosis-like reaction may encompass fatigue, fever, weight loss, joint pain, skin rash, and leg swelling. Diagnosis is typically made through a combination of blood tests, imaging studies, and biopsy of the affected tissue (6,8). Renal biopsy can confirm the diagnosis, showing non-caseating granulomas and interstitial nephritis consistent with sarcoidosis. Diagnosing ICI-induced sarcoidosis-like granulomas can be challenging, as it requires ruling out other potential causes and considering the temporal relationship with ICI therapy (9,10). Imaging studies such as chest X-rays or CT scans may show characteristic findings such as enlarged lymph nodes or lung infiltrates. Biopsy samples from affected organs may reveal non-caseating granulomas, a hallmark feature of both sarcoidosis and ICI-induced sarcoidosis-like granulomas (11,12). Prompt recognition and management of ICI-associated sarcoidosis reaction is crucial to minimize kidney damage and improve outcomes. Treating renal sarcoidosis-like reaction involves stopping the PD-1 inhibitor and administering corticosteroids to reduce inflammation.

In severe cases, immunosuppressive drugs may also be used (4,9). Regarding treating this condition, recently, Charkviani et al, successfully treated a renal biopsy documented sarcoid-like non-caseating granulomas with a corticosteroid regimen (4). In another case report, Purcell et al, described a 50-year-old male with renal cell carcinoma who obtained lymphadenopathy and diffuse pulmonary opacification across nivolumab therapy, which was presumed sarcoid granulomatous inflammatory reaction due to immunotherapy. In their case, the immunotherapy was continued without the development of sarcoidosis or clinical worsening of the patient (13). Moreover, Chanson et al, characterized 32 cases with biopsy-defined sarcoidosis, with a median time of 3 months (range, 2-29 months) between initiation of ICIs therapy and sarcoidosis diagnosis. They found that combined ICI therapy was accompanied by a shorter delay in developing sarcoidosis symptoms. This study showed that the disease was symptomatic in 59% of cases, with mainly general, cutaneous, and respiratory symptoms. The organs involved comprised mostly the mediastinal lymph nodes, the lungs, and the skin, followed by the eyes. They concluded that this condition is probably more benign than that of idiopathic sarcoidosis and does not essentially indicate ICI discontinuation (14).

Conclusion

Immune checkpoint inhibitors targeting PD-1, programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have demonstrated remarkable efficacy in various malignancies. However, these agents can disrupt immune tolerance mechanisms, potentially leading to autoimmune-like adverse events. Among these events, sarcoidosis-like reactions have been reported in multiple organs, including the lungs, skin, liver, and kidneys. While renal involvement is relatively uncommon, it can significantly affect patient management and outcomes.

Authors' contribution

Conceptualization: Parisa Keshtgar, Samin Karamian.
Data curation: Samin Karamian.
Investigation: Parisa Keshtgar, Samin Karamian.
Resources: Parisa Keshtgar.
Supervision: Parisa Keshtgar, Samin Karamian.
Validation: Samin Karamian.
Visualization: Samin Karamian.
Writing—original draft: Parisa Keshtgar, Samin Karamian.
Writing—review and editing: Parisa Kaviani, Payam Peymani, Neda Kianpour.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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