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Immune checkpoint inhibitors and IgA nephropathy; A rare side effect

Maryam Dehghani Mobarakeh[1], **Ahmadreza Maghsoudi**[2*]

[1]Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

The pathophysiological mechanisms of secondary IgA nephropathy (IgAN) containing IgA-mediated immune complex deposition in the glomeruli. However, the specific triggers can vary widely, including infections, liver disease, and malignancies, in addition to drug-induced factors. IgAN is a rare however is a serious complication of immune checkpoint inhibitor (ICI) therapy that can lead to acute kidney injury. Clinically, the diagnosis of sIgAN typically follows a temporal association between medication administration and the onset of renal symptoms, such as hematuria or proteinuria. A kidney biopsy is often necessary to confirm the diagnosis and rule out other causes of nephropathy.

Mini-Review

Implication for health policy/practice/research/medical education:
Primary IgAN is a complex interplay of genetic and environmental factors that lead to the production of galactose-deficient IgA1 and formation of immune complexes. However, the pathogenic mechanisms in secondary IgAN are less well-defined but may involve drug-induced immune dysregulation and inflammation. Immune checkpoint inhibitor (ICI)-associated IgAN is uncommon; however, anti-PD-1 inhibitors are the most commonly associated ICIs with IgA nephropathy, although the overall risk remains low and may be influenced by individual patient factors.

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Introduction

Secondary IgA nephropathy (IgAN) is a type of kidney disease that arises due to various underlying conditions or factors, including certain medications (1). It is possible that, induction of an immune response that leads to the deposition of IgA in the kidneys, resulting in this condition. For example, medications such as TNF-α inhibitors and IL-12/IL-23 inhibitors have been implicated in the development of secondary IgAN (1,2). These drugs are commonly used in the treatment of autoimmune diseases and can alter immune responses, potentially leading to kidney damage (2). Additionally bevacizumab, a monoclonal antibody used in cancer therapy, has been reported to induce secondary IgAN in some patients (3). There are reports on oral anticoagulants, which can contribute to the development of secondary IgAN by affecting the immune system and renal function (3). Moreover, thioureylene derivatives, which are administered in the treatment of hyperthyroidism, have been noted as potential triggers for secondary IgAN (1,3). While IgAN is the most common primary glomerulonephritis throughout world (4), only a few cases secondary to immune checkpoint inhibitors (ICIs) treatment have been described. In this mini-review we focus to the IgAN following the administration of ICIs.

Search strategy

For this brief review, we conducted a search on several databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, the Directory of Open Access Journals (DOAJ), and Embase. Our search utilized various keywords such as IgA nephropathy, immune checkpoint inhibitors, ICI-associated IgAN, and IgA deposition.

***Corresponding author**: Ahmadreza maghsoudi, Email: dr_maghsoudi_md@yahoo.com

Glomerular diseases linked with ICIs

The majority of individuals experiencing ICI-related glomerulopathy were treated with anti-PD-1 antibodies, which were involved in 71.4% of the cases (5). In addition, Pauci-immune GN accounts for approximately 27%-28% of cases. It is characterized by the absence of significant immune complex deposition (5,6). Besides, podocytopathies, such as minimal change disease and focal segmental glomerulosclerosis, represent about 24-26% of cases (5,6). Previous reports showed the presence of C3 glomerulonephritis which is noted in around 11-19% of cases (5-8). Other less common types are immune-complex glomerulonephritis (18.9%), renal vasculitis, often reported alongside pauci-immune GN, thrombotic microangiopathy (6,9). However, acute interstitial nephritis remains the most frequent kidney immune-related adverse event, while glomerular lesions are also increasingly being recognized (9).

IgA nephropathy associated with ICIs

IgA nephropathy has been reported as a rare complication following administration of ICIs, typically occurring within 1-12 months after initiating of these agents (9). The incidence appears to be much lower compared to acute tubulointerstitial nephritis, another common kidney complication of this group (9). The mechanisms by which ICIs trigger IgAN containing the induction of autoimmunity and loss of tolerance to IgA leading to IgA deposition, in addition to the increased production of IgA immune complexes due to enhanced B cell activation (5,8). Prior studies revealed an increased mucosal inflammation following the administration of ICIs which leads to increased IgA production and deposition (5,8,11). Patients with ICI-associated IgAN usually present with acute kidney injury, hematuria, and proteinuria. Kidney biopsy findings include mesangial IgA deposits, endocapillary hypercellularity, and segmental glomerulosclerosis, concomitant acute tubulointerstitial nephritis is often present to varying degrees (10-12).

Clinical findings of IgAN-associated ICIs

Prior cases reports have shown that, ICIs have been associated with the development of IgAN, although the incidence remains low compared to other renal complications like acute tubulointerstitial nephritis (10,13). Among the ICIs, anti-PD-1 antibodies, such as pembrolizumab and nivolumab, have been most frequently implicated in cases of ICI-related IgAN (5,8,10). Reports indicate that IgAN can manifest within some months after initiating therapy with these agents, with varying severity and typically managed by corticosteroids and discontinuation of the ICI (5,8,10). While the overall incidence of IgAN following ICI therapy is rare, it is suggested that it may be underdiagnosed due to its often mild presentation, which can include only microscopic hematuria or low levels of proteinuria (10).

The mechanism responsible ICI-induced IgAN may involve a breakdown of immune tolerance and aberrant immune responses, particularly in patients with pre-existing conditions that predispose them to kidney disease (10,14). Recently, Chabannes et al reported a case of severe IgAN associated with ICI therapy in a 65-year-old male with non-small cell lung carcinoma (10). The patient developed a severe acute kidney injury with a significant increase in creatinine levels three weeks after the second course of chemotherapy combined with ICI. A renal biopsy was performed, which revealed significant proliferative lesions in 80% of the glomeruli, consisting of mesangial proliferation, endocapillary hypercellularity, crescents along with intense mesangial IgA deposits with co-deposition of C3, without fibrinogen deposits (10).

Management of IgAN-associated ICIs

Treatment of secondary IgAN generally requires discontinuation of the causative medication and supportive care (15). Treatment typically involves discontinuation of the offending ICI and initiation of corticosteroids (16). Renal outcomes are variable, with some cases showing recovery of renal function and reduction in proteinuria with treatment, while others progress to chronic kidney disease (15,16).

Conclusion

Secondary IgAN is an important consideration in patients with renal impairment, particularly those undergoing treatment with specific medications. IgAN is a rare but serious complication of ICI therapy that can lead to acute kidney injury. Clinically, the diagnosis of sIgAN typically follows a temporal association between medication administration and the onset of renal symptoms, such as hematuria or proteinuria. A kidney biopsy is often necessary to confirm the diagnosis and rule out other causes of nephropathy.

Authors' contribution

Conceptualization: Ahmadreza Maghsoudi.
Validation: Ahmadreza Maghsoudi.
Investigation: Ahmadreza Maghsoudi.
Resources: Maryam Dehghani Mobarakeh.
Data curation: Ahmadreza Maghsoudi.
Visualization: Maryam Dehghani Mobarakeh.
Supervision: Ahmadreza Maghsoudi.
Writing–original draft: Ahmadreza Maghsoudi
Writing–review and editing: Maryam Dehghani Mobarakeh.

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.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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