



NEOADJUVANT IMMUNOTHERAPY AS A RISK FACTOR FOR HASHIMOTO'S DISEASE

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Study performed Postgraduate Program in Biotechnology at Potiguar University/ UnP. Financial support: None.

Conflicts of interest: None.

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Submitted: may 13; accepted after revision, dec 20, 2024.

ABSTRACT

This review investigates the association between neoadjuvant immunotherapy and the onset of Hashimoto's disease in patients with neoplastic conditions. With the increasing use of immunotherapy in oncology, understanding potential immune-related adverse events, particularly autoimmune thyroiditis, is crucial for optimizing patient outcomes and managing therapy-related risks. Our findings suggest a notable incidence of Hashimoto's disease among cancer patients receiving neoadjuvant immunotherapy. The underlying mechanisms may involve immune checkpoint inhibitors disrupting immune tolerance, leading to autoimmune thyroiditis. This review highlights the need for vigilant monitoring of thyroid function in patients undergoing immunotherapy and suggests potential strategies for early detection and management of Hashimoto's disease in this population. Further research is required to elucidate the precise mechanisms and risk factors involved, which could inform clinical guidelines and improve patient care.

Keywords: immunotherapy, Hashimoto disease, autoimmune thyroiditis, neoadjuvant therapy, adverse drug reactions

INTRODUCTION

The advent of neoadjuvant immunotherapy has significantly improved the prognosis for patients with various types of cancer. This therapeutic approach involves administering immunotherapeutic agents before the primary treatment, such as surgery, to enhance the body's immune response against tumor cells¹⁻³.

However, while neoadjuvant immunotherapy has shown remarkable efficacy in reducing tumor burden and improving survival rates, it is also associated with a spectrum of immune-related adverse events (irAEs), including the induction of autoimmune diseases like Hashimoto's thyroiditis⁴⁻⁷.

Hashimoto's thyroiditis is a chronic autoimmune disease characterized by the destruction of thyroid gland tissue, leading to hypothyroidism. The pathogenesis of Hashimoto's disease involves a complex interplay of genetic predisposition and environmental factors that trigger an immune response against thyroid antigens⁸⁻¹⁰.

With the increasing use of immunotherapies, there is growing evidence that these treatments can exacerbate or trigger autoimmune responses, including those affecting the thyroid¹¹.

Checkpoint inhibitors, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, are among the most used immunotherapies in the neoadjuvant setting. These agents block inhibitory pathways in T cells, thereby enhancing the immune system's ability to attack cancer cells¹²⁻¹⁴.

Nonetheless, amplifying immune responses can also disrupt immune tolerance, leading to autoimmunity. This mechanism is believed to underlie the development of thyroiditis and other autoimmune conditions in patients undergoing checkpoint inhibitor therapy¹⁵⁻¹⁷.

The incidence of thyroid dysfunction, particularly hypothyroidism due to thyroiditis, is notably higher in patients treated with checkpoint inhibitors compared to those receiving other cancer therapies¹⁸. Clinical studies have reported that up to 20% of patients on anti-PD-1 or anti-PD-L1 therapies develop thyroiditis, with a subset progressing to permanent hypothyroidism requiring lifelong thyroid hormone replacement¹⁹.

The clinical presentation of ICI-induced Hashimoto's thyroiditis can vary but typically includes symptoms of hypothyroidism such as fatigue, weight gain, cold intolerance, and dry skin²⁰.

These symptoms can significantly impact patients' quality of life and may complicate cancer treatment protocols. Therefore, early identification and management of thyroid dysfunction in neoadjuvant immunotherapy patients are critical²¹.

Diagnosis of ICI-induced Hashimoto's thyroiditis involves a combination of clinical evaluation, laboratory testing, and imaging. Vital diagnostic tests include serum TSH, free T4, and free T3 levels and the detection of thyroid autoantibodies such as anti-TPO and anti-Tg. A thyroid ultrasound may also assess glandular inflammation and structural changes²²⁻²⁴.

Managing thyroiditis in the context of neoadjuvant immunotherapy requires a multidisciplinary approach. Endocrinologists, oncologists, and primary care physicians must collaborate to monitor thyroid function closely and adjust treatment plans as needed²⁵⁻²⁷.

For patients who develop hypothyroidism, levothyroxine replacement therapy is the standard of care. The thyroid hormone replacement dosage should be tailored to maintain TSH levels within the normal range, minimizing symptoms and optimizing overall health²⁸⁻³⁰.

The pathophysiological mechanisms underlying ICI-induced thyroiditis are still under investigation. It is hypothesized that the blockade of PD-1, PD-L1, and CTLA-4 pathways disrupts immune homeostasis, leading to an autoreactive immune response against thyroid antigens³⁰⁻³³.

Genetic factors may also play a role, as specific HLA haplotypes are associated with a higher risk of autoimmune thyroid disease. Environmental factors such as viral infections and iodine intake could modulate immune responses in susceptible individuals³⁴⁻³⁶.

Research into predictive biomarkers for ICI-induced thyroiditis is ongoing. Identifying patients at risk before initiating immunotherapy could allow for proactive monitoring and early intervention³⁷. Potential biomarkers include baseline thyroid autoantibody levels, genetic markers, and specific cytokine profiles. Further studies are needed to validate these biomarkers and integrate them into clinical practice³⁸.

Preventive strategies to mitigate the risk of thyroiditis in patients undergoing neoadjuvant immunotherapy are also being explored. These strategies include immunomodulatory agents that selectively target pathways involved in autoimmunity while preserving antitumor immunity. Personalized treatment plans based on genetic and immunological profiling may help reduce the incidence of irAEs³⁹⁻⁴¹.

Neoadjuvant immunotherapy represents a double-edged sword in cancer treatment, offering substantial therapeutic benefits while posing risks for autoimmune diseases such as Hashimoto's thyroiditis⁴².

Integrating vigilant monitoring, early diagnosis, and comprehensive management strategies is essential to optimize patient outcomes and minimize adverse effects. Continued research is crucial to unravel the complex mechanisms of ICI-induced autoimmunity and develop targeted interventions to safeguard patient health⁴³⁻⁴⁵.

This review aims to investigate the association between neoadjuvant immunotherapy and the development of Hashimoto's disease in neoplastic patients. This review aims to comprehensively understand the underlying pathophysiological mechanisms, incidence, and clinical presentation of immune checkpoint inhibitor (ICI)-induced thyroiditis. It seeks to outline the diagnostic and management strategies for this condition^{39,40}.

The review intends to identify predictive biomarkers and discuss potential preventive and therapeutic approaches to mitigate immune-related adverse events associated with immunotherapy in cancer patients. Through this analysis, the goal is to optimize oncological treatment and improve the quality of life for patients while maintaining the therapeutic efficacy of ICIs.

METHODS

The research methodology for this review was designed to thoroughly investigate the potential link between neoadjuvant immunotherapy and the onset of Hashimoto's disease in patients with neoplastic conditions. The study utilized multiple reputable databases, including PubMed, Scopus, SciELO, Embase, and Web of Science, ensuring a comprehensive coverage of relevant scientific and medical literature. These databases are recognized for their extensive collections of peer-reviewed publications. Google Scholar was employed to access gray literature, which often includes significant studies not available in standard academic journals. The primary objective was to understand the incidence and underlying mechanisms of Hashimoto's disease as a possible adverse effect of neoadjuvant immunotherapy in cancer patients. To achieve this, search parameters were carefully crafted using relevant keywords such as "Immunotherapy," "Hashimoto Disease," "Autoimmune Thyroiditis," "Neoadjuvant Therapy," and "Adverse Drug Reactions." This strategic combination of search terms ensured the retrieval of studies directly pertinent to the research objectives. Inclusion criteria encompassed a broad spectrum of study designs, including randomized controlled trials, cohort studies, case-control studies, systematic reviews, and meta-analyses. This approach aimed to capture diverse evidence and perspectives regarding the association between neoadjuvant immunotherapy and Hashimoto's disease. Exclusion criteria were also established to filter out studies on unrelated pathologies, non-immunotherapy treatments, or other autoimmune diseases. Two independent reviewers initially screened each study's title and abstract for relevance and compliance with predefined criteria to ensure methodological rigor. Any discrepancies between the reviewers were resolved through consultation with a third reviewer, thereby minimizing bias and ensuring consistent selection. This dual-review process ensured that the final dataset comprised studies meeting the highest standards of relevance and quality. This systematic approach to the literature review provided a solid foundation for evaluating and synthesizing the findings. It ensured that the conclusions of this study were based on a comprehensive and critically assessed body of scientific evidence regarding

neoadjuvant immunotherapy as a risk factor for Hashimoto's disease in neoplastic patients..

RESULTS AND DISCUSSION

Table 1 – Immunotherapy Agents and risk of Hashimoto's Thyroiditis

Immunotherapy Agent	Types of Tumors	Risk Factor for Hashimoto's Thyroiditis and Molecular Mechanism
Pembrolizumab (anti-PD-1)	Melanoma, non-small cell lung cancer, Hodgkin lymphoma, Bladder cancer, Head and neck cancer	Blocking PD-1 leads to excessive T-cell activation, causing autoimmune destruction of thyroid cells.
Nivolumab (anti-PD-1)	Melanoma, non-small cell lung cancer, Renal cell carcinoma, Hodgkin lymphoma, Esophageal cancer	Inhibition of PD-1 increases immune activity, potentially resulting in lymphocytic infiltration of the thyroid.
Ipilimumab (anti-CTLA-4)	Melanoma, non-small cell lung cancer, Renal cell carcinoma	Inhibition of CTLA-4 removes the brakes on T-cells, promoting autoimmunity and thyroid inflammation.
Atezolizumab (anti-PD-L1)	Non-small cell lung cancer, Bladder cancer, Renal cell carcinoma	Inhibition of PD-L1 can trigger autoimmune responses, including thyroid cell destruction by activated lymphocytes.
Durvalumab (anti-PD-L1)	Non-small cell lung cancer, Bladder cancer	Similar to Atezolizumab, it may promote autoimmunity by releasing inhibition on T-cells, leading to thyroid inflammation.
Avelumab (anti-PD-L1)	Merkel cell carcinoma, Urothelial carcinoma	Blocking PD-L1 can cause immune dysfunction and autoimmunity, including effects on the thyroid.
Cemiplimab (anti-PD-1)	Cutaneous squamous cell carcinoma	Inhibition of PD-1 can result in uncontrolled immune activation, leading to autoimmune responses against the thyroid.
Tremelimumab (anti-CTLA-4)	Hepatocellular carcinoma, Mesothelioma	Inhibition of CTLA-4 can provoke autoimmune responses by prolonged T-cell activation, affecting the thyroid.

The association between neoadjuvant immunotherapy and the development of Hashimoto's disease in neoplastic patients represents a critical area of investigation, given the increasing use of immune checkpoint inhibitors (ICIs) in cancer treatment⁴¹. The pathophysiology of ICI-induced thyroiditis, including Hashimoto's thyroiditis, involves complex immune mechanisms that need further elucidation¹².

Immune checkpoint inhibitors, such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, enhance the immune response against tumors by blocking inhibitory signals that restrain T-cell activity¹⁶. While effective against cancer cells, this immune activation can also target self-antigens, leading to autoimmunity⁴².

Thyroiditis is one of the most common endocrine adverse events associated with ICIs, with mechanisms thought to involve both direct immune activation and indirect effects through cytokine release and inflammation⁴³.

Specific risk factors for developing ICI-induced thyroiditis include preexisting thyroid autoimmunity, a history of autoimmune diseases, and the type and dosage of ICIs used⁴⁴. Patients with baseline thyroid antibodies, such as anti-thyroglobulin and anti-thyroid peroxidase, are at increased risk. Genetic predispositions, such as specific HLA haplotypes, may also play a role in susceptibility⁴⁵.

Biomarkers that can predict the development of immune-related adverse events (irAEs), including thyroiditis, are of significant interest. Elevated levels of thyroid antibodies before initiating ICI therapy can indicate a higher risk of thyroid dysfunction^{46,47}.

Serum cytokine profiles and specific genetic markers, such as single nucleotide polymorphisms (SNPs) in immune-related genes, may serve as predictive biomarkers²⁸.

Further research is needed to unravel the complex mechanisms of ICI-induced autoimmunity and develop targeted interventions to safeguard patient health. Understanding the interplay between different immune cells, cytokines, and genetic factors is crucial⁴⁸⁻⁵⁰.

Advanced omics technologies, including genomics, proteomics, and metabolomics, can provide insights into the molecular pathways involved in ICI-induced thyroiditis⁵¹.

Preventive measures before initiating immunotherapy are essential to reduce the risk of thyroiditis. Regular screening for thyroid function and autoantibodies can help identify high-risk patients⁵².

Prophylactic use of immunosuppressive agents or anti-inflammatory medications in selected patients may also be considered, although this approach requires careful balancing of risks and benefits⁵³.

The long-term prognosis for patients who develop ICI-induced Hashimoto's thyroiditis varies. While some patients may achieve stable thyroid function with hormone replacement therapy, others may experience persistent hypothyroidism or fluctuating thyroid function. Follow-up and management are crucial to monitor thyroid function and adjust treatment as needed⁵⁴⁻⁵⁶.

There are still significant gaps in the understanding of ICI-induced thyroiditis. More studies are needed to determine the precise mechanisms of immune activation and tolerance breakdown³⁹. Researchers should focus on identifying patient-specific factors contributing to susceptibility and developing personalized therapeutic strategies⁵⁷.

Current diagnostic approaches for ICI-induced thyroiditis include thyroid function tests, imaging studies, and histopathological evaluation when necessary. Early detection and prompt intervention are essential to manage symptoms and prevent complications⁵⁸.

Management of ICI-induced thyroiditis involves hormone replacement therapy for hypothyroidism and close monitoring of thyroid function during and after immunotherapy⁴⁴. In cases of hyperthyroidism, antithyroid medications or beta-blockers may be used to control symptoms. Collaboration between oncologists and endocrinologists is vital for optimal patient care⁵⁹.

The impact of ICI-induced thyroiditis on cancer treatment outcomes is an important consideration. While ICIs can significantly improve survival rates in cancer patients, the occurrence of irAEs, including thyroiditis, may necessitate therapy adjustments. Understanding the balance between effective cancer control and the management of adverse effects is crucial⁶⁰⁻⁶².

Future research should also explore the potential benefits of combining ICIs with other therapeutic modalities, such as targeted therapies or conventional chemotherapy, to enhance efficacy while minimizing adverse effects⁶³. Investigating the role of combination therapies in modulating immune responses and reducing autoimmunity is a promising area of study⁶⁴.

Neoadjuvant immunotherapy presents opportunities and challenges in treating neoplastic patients. While ICIs have revolutionized cancer therapy, their association with autoimmune conditions like Hashimoto's thyroiditis necessitates a deeper understanding of the underlying mechanisms, risk factors, and effective management strategies^{65,66}.

CONCLUSION

In conclusion, the relationship between neoadjuvant immunotherapy and the development of Hashimoto's disease in cancer patients underscores the need for comprehensive monitoring and management strategies. Identifying at-risk patients through biomarkers and genetic screening can help tailor preventive measures and therapeutic interventions. Continued research into the pathophysiological mechanisms and long-term outcomes of ICI-induced thyroiditis is essential to optimize cancer treatment while safeguarding patient health.

This review highlights the importance of multidisciplinary collaboration in managing the complexities of cancer immunotherapy and its associated autoimmune effects, ultimately aiming to improve patient outcomes and quality of life.

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