Editorial paper

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# The relationship between immunoglobulin G4-related disease and malignancy

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Immunoglobulin G4-related disease (IgG4-RD) has emerged over the past two decades as a distinct systemic fibroinflammatory condition characterized by lymphoplasmacytic infiltration and elevated serum IgG4 levels [1, 2]. It affects multiple organs, manifesting in various forms such as autoimmune pancreatitis (AIP), sclerosing cholangitis, and retroperitoneal fibrosis. Although diagnostic criteria and treatment approaches have evolved, questions about their association with malignancies remain a pressing concern. Immunoglobulin G4-related disease is recognized as a clinical entity that can mimic malignancy, is associated with an increased risk of cancer, and may contribute to malignancy development through the use of immunosuppressive therapies. This editorial concisely surveys the state of knowledge on these associations.

In IgG4-RD, the results of infiltrating IgG4-positive plasma in IgG4-RD can mimic malignancies both clinically and radiologically, presenting challenges for accurate diagnosis. For instance, lesions in the pancreas, thyroid, or lymph nodes may resemble cancerous tumours on imaging. Misdiagnosis can lead to unnecessary surgical interventions or delays in appropriate treatment. Therefore, clinicians must consider IgG4-RD in differential diagnoses of malignancies, especially in patients with multi-organ involvement or atypical presentation. Biopsy and histopathological evaluation showing lymphoplasmacytic infiltration and storiform fibrosis are crucial for distinguishing IgG4-RD from cancer [3, 4].

Early detection and management of malignancies in IgG4-RD patients are crucial for improving outcomes and understanding this complex relationship [5]. Immunoglobulin G4-related disease occurs particularly in older populations, in which malignancies occur more often. However, it has been suggested that patients with IgG4-RD face an independent elevated risk of malignancies compared to the general population [6]. The meta-analysis by Yu et al. [6] pooled data from 10 studies spanning 2003 to 2020, encompassing 1,747 patients with IgG4-RD. After adding the recent data of nearly 4,000 patients, the estimated standardized incidence ratio of malignancies reaches as high as 6.3, indicating more than 6 times the risk compared to non-IgG4-RD individuals [7–12]. Malignancies may appear before and after diagnosis of IgG4-RD, peaking at the time of diagnosis, with about 50% [11, 12]. The duration of the observational period in these studies may influence these data, since the last 2 larger studies include long-term data of registries [11, 12].

The association with malignancies is particularly pronounced for pancreatic cancer and lymphoma, while the risk for other cancers such as lung cancer, gastric malignancies, bladder and renal cancer and ENT (ear, nose and throat) cancers is less pronounced [6, 8, 11].

Elevated serum IgG4 levels are associated with an increased risk of disease progression, especially in melanoma [13]. Studies indicate that high IgG4 levels correlate with poorer progression-free survival and overall survival, particularly in early-stage melanoma. Immunoglobulin G4 may promote immunosuppressive mechanisms, reducing the effectiveness of anti-tumour immune responses. This biomarker also appears elevated in some other malignancies, suggesting a potential link between IgG4 and cancer progression beyond melanoma. Studies also demonstrated that while elevated serum IgG4 levels are more common in AIP (65%) compared to pancreatic cancer (10.4%), mild elevations cannot reliably distinguish between the 2 conditions [14]. Notably, elevations exceeding twice the upper limit of normal are more frequently observed in AIP. Further research could clarify its role in malignancies and improve prognostic tools for personalized treatments.

Several theories have been proposed to describe the underlying mechanism of the increased risk of malignan-

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cies. Chronic inflammatory states and immune dysregulation are well-known promoters of carcinogenesis. In IgG4-RD, persistent inflammation mediated by T-helper type 2 cells and regulatory T-cells leads to increased levels of cytokines such as interleukin-4 (IL-4), IL-10, and transforming growth factor β, which can drive cellular proliferation and fibrosis. These cytokines may also induce genomic instability, fostering a microenvironment conducive to tumorigenesis. Furthermore, studies suggest that IgG4-RD may be a paraneoplastic syndrome, where malignancies trigger an inflammatory response. This is supported by observations that IgG4-RD sometimes resolves after successful cancer treatment [9]. Also, the immunosuppressive therapy used in the treatment of IgG4-RD may play a role. This treatment could theoretically increase cancer risk by impairing immune surveillance. However, existing data have not conclusively linked these therapies to heightened malignancy incidence. Further longitudinal studies are needed to clarify this potential risk.

Given the possible link between IgG4-RD and malignancy, clinicians should adopt a proactive approach to cancer screening in these patients, especially for pancreatic and hematologic malignancies. Early detection strategies might include routine imaging and serum tumour markers, particularly in patients presenting with atypical symptoms or rapid disease progression. While current evidence points to an association between IgG4-RD and certain cancers, significant gaps remain. Future research should focus on longer follow-up periods and standardized diagnostic criteria to accurately assess cancer risk. Studies are also required to identify biomarkers to identify malignancy-related inflammation that could enhance diagnostic accuracy.

In conclusion, the relationship between IgG4-RD and malignancy is complex and multifaceted, with emerging evidence suggesting a higher risk for certain cancers. While the exact mechanisms remain unclear, the implications for patient management are significant. Careful and lifelong monitoring, early intervention, and continued research are essential to unravel this connection and improve outcomes for IgG4-RD patients.

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