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Laboratory Evaluation of Primary Immunodeficiencies from Secondary Immunodeficiencies in the Context of Hematological Malignancies: Review

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Abstract

Primary immunodeficiencies (PIDs) represent a diverse group of congenital disorders characterized by defects in the immune system. Distinguishing PIDs from secondary immunodeficiencies (SIDs) is critical, particularly in patients with hematological malignancies, as misdiagnosis can lead to inadequate treatment and poor patient outcomes.This review synthesizes case studies and recent literature to explore the clinical overlap between PIDs, SIDs, and hematological malignancies. A comprehensive search of national databases and clinical guidelines was conducted to analyze patterns in diagnosis, treatment strategies, and the implications of immunodeficiency in cancer prognosis.Findings indicate that a significant proportion of patients with hematological malignancies also exhibit signs of immunodeficiency, complicating diagnosis. Case studies highlight instances where SIDs obscure underlying PIDs, particularly in patients treated with immunosuppressive therapies such as rituximab. The review underscores the importance of early immunological evaluation in patients with recurrent infections and malignancies.The differentiation between PIDs and SIDs is paramount for optimizing patient management and therapeutic interventions. Enhanced awareness and interdisciplinary approaches are essential in the timely identification of PIDs, particularly in patients presenting with hematological malignancies. Future research should focus on developing standardized screening protocols for immunodeficiencies in oncology settings to improve patient outcomes.

Keywords: *Primary Immunodeficiency, Secondary Immunodeficiency, Hematological Malignancies, Immunological Evaluation, Cancer Prognosis.*

Introduction

Primary immunodeficiencies (PIDs), a diverse category of congenital immune disorders, are established at birth but may develop throughout time, resulting in a range of clinical and laboratory manifestations. The International Union of Immunological Societies categorizes them into ten distinct classes based on the primary immune compartments and functions impacted, which encompass combined immunodeficiencies (T- and B-cell defects) with or without syndromic characteristics, antibody deficiencies (B-cell defects), and immune dysregulation (impaired regulation and/or abnormal activation of immune subsets) (1).

Conversely, secondary immunodeficiencies (SIDs) are acquired reductions in immune cell numbers and/or functionality. The predominant form of SID is a diminished antibody level resulting from an underlying illness or as an adverse impact of pharmacological treatments for hematological malignancies and

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autoimmune disorders (2, 3). Ironically, immunological deficits previously ascribed to secondary factors may partially stem from an underlying primary immunodeficiency. In the age of immune-modulating biologics, it is crucial to differentiate between primary and secondary antibody deficits.

Both Primary Immunodeficiencies (PIDs) and Secondary Immunodeficiencies (SIDs) may be linked to infections, immunological dysregulation, autoimmune diseases, lymphoproliferation, and malignancies, complicating the elucidation of their interrelationships in clinical practice (4). A study examining the initial clinical manifestations of confirmed PID revealed that the majority of patients (68%) had a history of infection; however, an exclusive emphasis on infection-related manifestations would have overlooked a significant number of patients who initially exhibited alternative findings, such as immune dysregulation (5). Patients with primary immunodeficiency (PID) are recognized to have an elevated risk of hematological malignancies and autoimmune diseases (6, 7). Conversely, SID may arise as a result of B-cell lymphoproliferative disorders, including multiple myeloma and chronic lymphocytic leukemia (CLL) (3, 8). Moreover, immune modulators, including B-cell depleting treatments and checkpoint inhibitors used in the treatment of hematological and autoimmune illnesses, may induce acute or sustained SID (9, 10).

This research examines case histories to investigate clinical overlaps between primary immunodeficiencies (PID), secondary immunodeficiencies (SID), hematological malignancies, and autoimmune illnesses, as well as the problems in distinguishing PID from SID and in formulating appropriate treatment regimens.

Intersections Among SID, PID, and B-Cell Lymphoproliferative Disorder

The example of a patient with follicular lymphoma with immunodeficiency illustrates the diagnostic challenges doctors have in distinguishing between primary immunodeficiency (PID) and secondary immunodeficiency (SID). A 67-year-old female patient arrived at the Emergency Department in 2003 with severe abdominal discomfort. She had a history of recurrent respiratory infections from infancy, one instance of pneumonia, and hypertension. Physical examination and imaging identified numerous lymphadenopathies in several locations, including the lung and bone marrow, while an inguinal node biopsy confirmed stage IV-B follicular lymphoma. She completed five rounds of chemotherapy with fludarabine, cyclophosphamide, and rituximab (FCR), attaining full remission in 2004. Upon her first evaluation, she had an osteolytic lesion in the L4 vertebra, accompanied by a soft tissue mass described as a peripheral nerve sheath tumor at the L4–L5 level, for which she received radiation therapy.

In 2006, she encountered a relapse of lymphoma, occurring within two years of diagnosis, which is an adverse prognostic indicator, and then underwent rituximab maintenance treatment for two years, resulting in full remission once again. In 2016, she was sent to the Immunology department for severe panhypogammaglobulinemia (low IgG, IgA, IgM) characterized by a complete loss of B cells, occurring in the context of lymphoma and severe infections. She was already undergoing intermittent immunoglobulin replacement treatment (IgRT). An immunological evaluation revealed a mostly humoral deficiency characterized by panhypogammaglobulinemia, with normal T cell and neutrophil numbers. Concerning functional antibody responses, after appropriate vaccinations, the patient exhibited measurable levels of anti-Pneumococcus (Pneumo-23) and anti-tetanus toxoid antibodies while undergoing immunoglobulin replacement therapy (IgRT). Nonetheless, these levels may be normal in patients undergoing intravenous immunoglobulin treatment, since the relevant antibodies are included in the administered product, making it difficult to differentiate the patient's intrinsic reaction to the vaccination. The reaction to anti-*Salmonella typhi* was minimal. This discovery was significant, since it included antibodies to *S. Typhi* that are undetectable in intravenous immunoglobulin preparations and hence do not affect plasma concentrations. Consequently, exposure to *S. typhi* antigen may assist in assessing functional antibody responses in individuals undergoing immunoglobulin replacement therapy (IgRT) (11). This indicated the existence of both quantitative (panhypogammaglobulinemia) and qualitative (low vaccination titer) antibody deficiencies.

The patient's clinical trajectory has fluctuated, characterized by recurrent pneumonia, herpes zoster, bacteremia, two secondary main neoplasms, and significant malabsorption. She has had inadequate humoral reconstitution while being in remission since 2008. She had a duodenal endoscopy due to frequent diarrhea, severe malnutrition, and low body weight, which indicated significant villous atrophy (Marsh grade 3b). A

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biopsy revealed intraepithelial lymphocytes and an absence of plasma cells. Upon analysis of the aggregate fraction of total intraepithelial lymphocytes, TCRγ/δ cells indicative of a celiac-like phenotype were absent, whereas normal levels of CD3 (T cells) and CD103 (tissue-resident memory T cells) were seen, with decreased iNKT, suggesting mucosal injury. The comprehensive assessment indicated a pronounced celiac-like enteropathy characterized by a unique immunophenotype. The occurrence of herpes zoster infections with enteropathy indicates immunological dysfunction and T cell dysregulation. This patient exhibited characteristics of mixed immunodeficiency with immunological dysregulation, in conjunction with humoral immunodeficiency. The follow-up of the patient's lymphoma, via the evaluation of serum-free light chains, revealed that kappa and lambda levels were almost undetectable until June 2021, when a sudden spike in kappa chains was seen. She is now undergoing evaluation for recurrence, 18 years post-onset of the original illness.

A 67-year-old woman exhibited follicular lymphoma, frequent respiratory illnesses since childhood, malabsorption, lymphoma recurrence within 2 years of onset, markedly low immunoglobulin levels, absence of B-cell reconstitution post-chemotherapy, non-infectious problems (enteropathy), two primary second neoplasms, and serious persistent infections despite immunoglobulin therapy, indicating potential T-cell dysfunction.

Exome analysis identified a homozygous variation in the LRBA gene, specifically (LRBA):c.3076C>T (p.Gln1026Ter). Functional data indicated that CTLA4 expression was lacking on the surface of activated T cells. LRBA deficiency is an autosomal recessive condition linked to a particular primary immunodeficiency, common varied immune deficiency (CVID), characterized by a range of mutations and significant variability in clinical and immunological features (12). A mixed immunodeficiency phenotype accompanied by enteropathy and malignancy may indicate a problem within the range of regulatory T-cell diseases (Tregopathy), including IPEX-like, CTLA4, and LRBA deficits. Consequently, we cannot exclude the possibility that this follicular lymphoma patient may possess an underlying primary immunodeficiency rather than a malignancy and/or drug-induced secondary immunodeficiency from anti-CD20 treatment (13, 14).

The example demonstrates how secondary immunodeficiency (SID) in the context of hematological malignancy may obscure an underlying primary immunodeficiency (PID). Consequently, it is essential to do immunodeficiency screening at the outset of malignancy. The following parts will mostly concentrate on CVID, a prevalent primary immunodeficiency disorder (15-19).

Hematological Cancer Screening for Common Fluctuating Immune Deficiency

The incidence of cancer is elevated in individuals with Common Variable Immunodeficiency (CVID), and a delayed diagnosis of CVID adversely affects cancer prognosis due to heightened infection risk and inadequate therapeutic response resulting from increased toxicity and recurrence. Patients diagnosed with cancer and possessing laboratory-confirmed immunological abnormalities, regardless of the presence of infections, have to undergo screening for Common Variable immunological Deficiency (CVID) and other immune deficiencies prior to the commencement of treatment. This will enable treating doctors to adjust therapy according to the underlying PID.

Screening for cancer in individuals with established CVID seems prudent; nevertheless, differentiating malignancy from lymphoproliferative disorders may be difficult. Additional comorbidities, such as inflammation, might further complicate the situation. No consensus recommendations exist for cancer screening and follow-up in these individuals. Furthermore, many authors have suggested a distinct histologic subclassification of lymphoma linked with PID (19). The methodology used must consider the need for biopsies and scans for diagnostic confirmation. An essential immunological assessment is crucial prior to initiating cancer treatment. Since either aspect of the issue, immunosuppression or hematopoietic malignancy may present first, it is crucial to employ an interdisciplinary strategy for the diagnosis and care of these individuals (3, 20–22).

Primary Immunodeficiency Associated with an Elevated Risk of Hematological Malignancies

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Immunodeficiency correlates with an elevated risk of cancer. PID presents a 1.4–5 times elevated risk of cancer relative to the general population, as shown by registry studies, while the absolute incidence remains modest (6, 23). The malignancy incidence among CVID patients is around ten percent (6, 23, 24), and lymphoproliferative disorders occur ten times more often in CVID than in the general population (25). Cancer is the 2nd leading cause of death in people with PID, behind infection (26). The aggregated prevalence of lymphoma is 4.1%, according to meta-analyses and registry-based research, whereas that of gastric cancer is 1.5 percent (16, 25).

Focusing on patients with hematological malignancies, which rank among the ten most prevalent cancer types, and lymphoproliferative disorders, there is a notable prevalence in immunocompromised persons, with germline alterations reported in 1–18% of cases according to early investigations (27). Approximately 20% of human malignancies are linked to chronic or latent infections, which are also more prevalent in immunocompromised individuals. Traditionally, 10% of hematological malignancies in pediatric patients are linked to congenital abnormalities; however, recent research using whole-exome sequencing identified genetically validated primary immunodeficiency in as much as 62 percent of kids with lymphoproliferative diseases (28, 29). This has therapeutic and prognostic significance, particularly for therapy choices. If lymphoproliferative diseases are equally prevalent in individuals with primary immunodeficiency (PID), this prompts an inquiry into the actual extent of PID within the global context of both malignant and non-malignant hematological lymphoproliferative illnesses (30).

CVID in the Context of Cancer

In the last two decades, we have acquired knowledge on the impact of infection-related malignancies, particularly the significance of chronic infections, with Helicobacter pylori, human papillomavirus, and hepatitis B and C estimated to account for 16% of all cancers globally (31). Numerous investigations have shown that lymphoma in primary immunodeficiency is often attributable to Epstein-Barr virus infections (19, 32, 33).

Cancer is a complicated multifactorial phenomenon, including both internal and extrinsic elements in its etiology. Multiple variables associated with carcinogenesis in CVID are shown in Figure 1 (34). Intrinsic factors include a genetically encoded impairment in the DNA repair machinery, abnormalities in T- and B-cell receptor (VDJ) or class switching recombination (Ig isotypes) as well as somatic hypermutation, as well as deficiencies in processes related to B-cell maturation and costimulatory signaling. Extrinsic causes include compromised immunosurveillance, dysbiosis, chronic mucosal inflammation, and diminished clearance of carcinogenic viral as well as bacterial illnesses, particularly *Helicobacter pylori* infection, and changing viral infections, such as Epstein-Barr virus infection.

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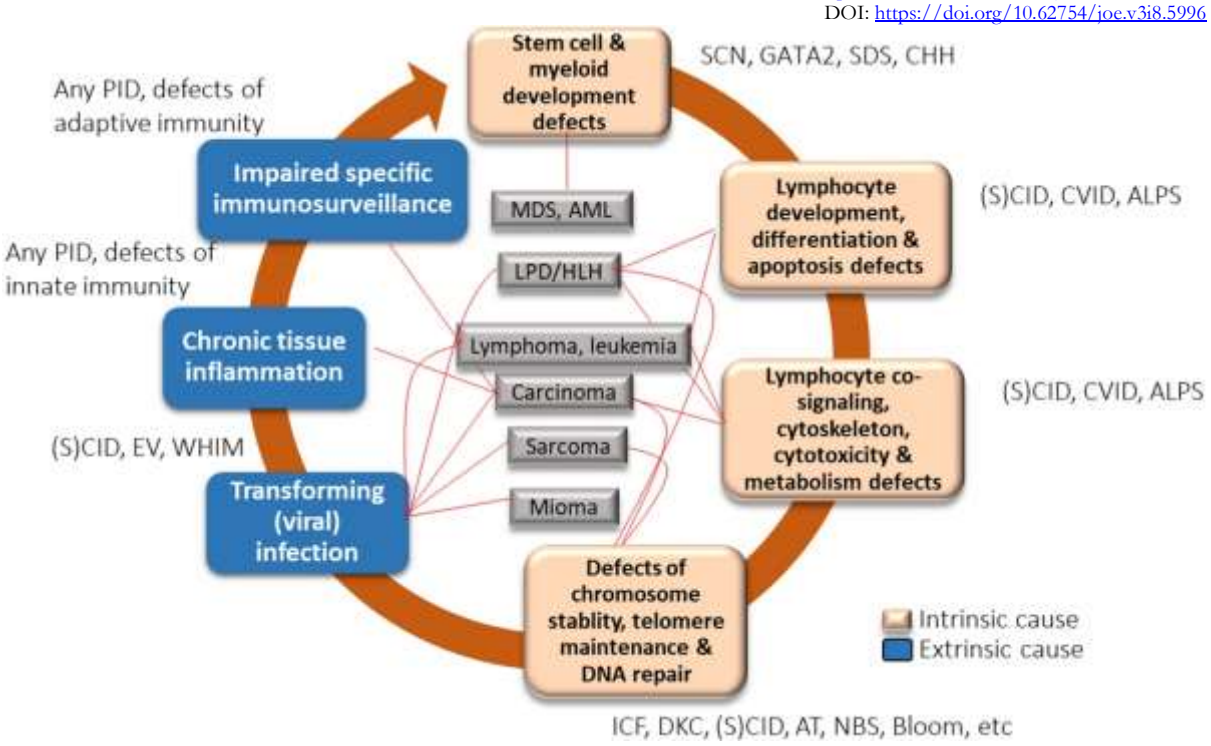

Figure 1. Factors Involved in Tumorigenesis in Common Varied Immune Deficiency (CVID) (34)

A comprehensive review and meta-analysis examining the incidence of malignancy in patients with Common Variable Immunodeficiency (CVID), derived from 48 studies, revealed a pooled malignancy prevalence of 8.6% (790 instances amongst 8123 CVID patients) (16). Lymphoma was the most prevalent malignancy, affecting 4% of individuals and representing 40% of all malignancies.

Non-Hodgkin Lymphoma and Genetic Alterations

Diffused large B-cell lymphoma (DLBCL) is the predominant hematological malignancy. The pursuit of germline mutations has introduced an additional degree of complication. A thorough examination of this subject reveals that, of 626 genes identified with somatic mutations in DLBCL, 24 have also been confirmed to possess harmful mutations in their germline form in DLBCL patients (27). Approximately one-third of the somatically altered genes identified in DLBCL are already associated with primary immunodeficiencies (e.g., ATM, DCLRE1C, PRKDC, IFNGR1, PIK3CD, PIK3R1, STAT3, FAS). A phenotypic analysis of 193 germline mutations across 211 somatically altered genes in DLBCL revealed that immunodeficiency was seen in 17% of instances (27). Preliminary studies indicate that hereditary mutations in DLBCL may exhibit distinct phenotypes, such as PID, which, in conjunction with environmental variables, might contribute to the development of lymphoma. Consequently, genetic methods may potentially detect PID in the context of lymphoma. Similar to other malignancies, enhanced genetic screening will uncover germline alterations that were first identified in somatically mutated lymphomas.

Encountering a CVID Patient: Indicators of Hematological Malignancy

In the management of a patient with CVID, some indicators may suggest an increased risk of lymphoma. Numerous research studies have analyzed CVID patients who had or did not have cancer to identify predictive indicators or clinical characteristics (16-19, 25, 26, 35–39). Identified potential risk factors included non-malignant lymphoproliferative illnesses, lymphadenopathy, autoimmune cytopenia, enteropathy, changed IgM levels, advanced age at CVID diagnosis, sex, late-onset paired immunodeficiency, germline genetic mutations, and susceptibility to Epstein-Barr virus.

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A meta-analysis of nine studies comparing demographic, clinical, and immunologic features among CVID individuals with and without malignancy revealed that malignancy patients were significantly older, exhibited elevated levels of IgG, IgA, and IgM (despite being lower than normal), and demonstrated a higher incidence of autoimmunity as well as malabsorption (16). Elevated IgM levels were correlated with lymphoid hyperplasia as well as lymphoid malignancies. Polyautoimmunity was seen in fifty percent of the patients. Numerous clinical and laboratory indicators may prompt clinicians to consider hematological malignancy in patients with CVID, particularly in the PIRD and late-onset CID categories, which must be differentiated from CVID.

Treatment Strategy for Antibody Deficit in SID Versus PID Individuals

The European expert consensus committee has provided guidelines for initiating IgRT in individuals with SID as well as hematological malignancies, including several factors such as hypogammaglobulinemia, infections, and vaccination responses (40). The criteria and corresponding algorithm resemble those used in patients with PID for the commencement of IgRT. Predicting which individuals with lymphoproliferative disorders are predisposed to developing SID and infections, hence necessitating IgRT, might be advantageous. Recently, the AAAAI Basic Immunodeficiency and Modified Immune Reaction Committees have developed practical advice for the diagnosis and therapy of secondary hypogammaglobulinemia. This comprehensive report addresses the absence of explicit guidelines regarding the initiation of IgRT and underscores the significance of age-specific reference ranges for pediatric patients, as well as the categorization of low IgG levels and the duration of hypogammaglobulinemia to ascertain the appropriate timing for IgRT (41).

A pertinent situation involves chronic lymphocytic leukemia (CLL), hypogammaglobulinemia, and the associated risk of infections. A Danish group has examined the parameters that predict SID in CLL and investigated potential biomarkers to ascertain the appropriate timing for initiating IgRT (57). They created a CLL Treatment-Infection Model (CLL-TIM) that forecasted which individuals were at elevated risk of treatment and/or infection within two years post-diagnosis. Machine learning algorithms were created with data from 4,149 patients, comprising 13 baseline assessments, 216 diagnoses, 153 pathology codes, 46 microbiological results, and 183 regular laboratory tests. Patients were categorized as high confidence/high risk, inadequate trust, and high confidence/low risk for infection (42, 43). The model failed to include information on immunoglobulins, unlike previous studies that have shown a correlation between substantial hypogammaglobulinemia (IgG <4g/L) or low IgG and IgA levels and an increased risk of severe infection (44, 45). The CLL-TIM algorithms indicated that the incidence of infections many years before the diagnosis of CLL was significantly predictive of the likelihood of infections occurring after diagnosis but before the initiation of CLL therapy. The authors determined that individualized risk variables may facilitate tailored treatment strategies for individuals with CLL, including the use of immunoglobulin (46).

Discussion

SID and PID crossovers provide difficulty for precise diagnosis and, therefore, suitable therapy. Considering the potential for immunological insufficiency in individuals with hematological malignancies or autoimmune diseases is crucial. Timely identification of PID will allow patients to obtain optimal treatment before end-organ damage occurs. Clinicians must take a comprehensive view; a history of recurrent infections, indications of immunological dysregulation, syndromic characteristics, cancer, and familial history may indicate primary immunodeficiency (PID).

Patients with hematological malignancies with immune deficiency are at elevated risk of poor prognosis owing to comorbidities such as infections and should be evaluated for primary immunodeficiency (PID) and secondary immunodeficiency (SID). An integrated method for early PID screening during the diagnosis of a lymphoproliferative illness has prognostic significance and may inform counseling for the patient and their family. In suspected instances, preliminary genetic analyses at the time of lymphoproliferative syndrome diagnosis are clinically significant. No consensus recommendations presently exist for cancer

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screening and follow-up in people with PID, a cohort recognized for its elevated cancer risk. International standards for malignancy screening and care in patients with PID are necessary.

Underlying primary immunodeficiency is prevalent in people with autoimmune cytopenia. Therapeutic approaches vary based on the etiology of the cytopenia. Furthermore, the administration of immune-modulating agents like rituximab or checkpoint inhibitors may uncover the existence of primary immunodeficiency (PID). Consequently, it is essential for doctors treating individuals with autoimmune cytopenia to contemplate the potential for primary immunodeficiency (PID).

A comprehensive immunological evaluation is essential for diagnosing primary immunodeficiencies (PIDs) and for monitoring biomarkers indicative of response to immune modulation, such as CD19hi21low B cells (age-associated B cells) and T follicular helper (Tfh) cells. It is crucial for individuals without a genetic diagnosis to detect any secondary immunological malfunction. Other writers have proposed that immunological profile-based grading systems may be beneficial (47).

Healthcare personnel managing patients with immunodeficiencies, particularly in hematology or oncology departments where first signs may be seen, must recognize the potential for Primary Immunodeficiency Disorders (PID) and Secondary Immunodeficiency Disorders (SID). A multidisciplinary approach is essential for the early identification and effective therapy of PID and SID in individuals with hematological malignancies or autoimmune diseases.

In summary, the many manifestations of primary immunodeficiencies (PIDs) suggest that antibody deficits formerly ascribed to secondary immunodeficiencies (SIDs) resulting from underlying diseases or therapeutic drugs used in the treatment of hematological cancers and autoimmune disorders may, in fact, stem from an underlying PID. Physicians must recognize the potential for SID and PID crossovers among individuals with blood-related cancers or autoimmune diseases.

Conclusion

In conclusion, the complexities surrounding primary and secondary immunodeficiencies necessitate a nuanced understanding of their clinical presentations, particularly in the context of hematological malignancies. The overlapping features of PIDs and SIDs can often lead to diagnostic challenges that may compromise patient care. This review highlights the necessity for healthcare providers to maintain a high index of suspicion for PIDs in patients exhibiting recurrent infections or other immunological dysregulation, especially those undergoing treatment for malignancies.

Moreover, the integration of genetic screening and advanced immunological assessments can significantly enhance the diagnostic accuracy for these conditions. Identifying underlying PIDs not only aids in formulating a comprehensive treatment plan but also informs prognostic discussions between clinicians and patients. Early detection and appropriate immunological intervention can mitigate complications arising from both the malignancy and the immunodeficiency, ultimately improving overall patient outcomes.

As the field of immunology continues to evolve, there is an increasing need for standardized protocols for screening and managing immunodeficiencies in patients with hematological malignancies. Collaborative efforts among immunologists, oncologists, and primary care providers are essential to establish effective management pathways. This multidisciplinary approach can facilitate timely interventions and tailored therapies that address both the malignancy and the underlying immunodeficiency.

In summary, recognizing and addressing the interplay between PIDs and SIDs is crucial for optimizing treatment strategies and improving prognoses for affected individuals. Future investigations should focus on refining diagnostic criteria and exploring innovative therapeutic options that consider the unique immunological profiles of these patients.

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التقييم المختبري لنقص المناعة الأولي مقابل نقص المناعة الثانوي في سياق الأورام الدموية: مراجعة

الملخص

الخلفية :تمثل نقص المناعة الأولي (Primary Immunodeficiencies - PIDs) مجموعة متنوعة من الاضطرابات الخلقية التي تتميز بعيوب في الجهاز المناعي. يعد التمييز بين نقص المناعة الأولي والثانوي (Secondary Immunodeficiencies - SIDs) أمرًا بالغ الأهمية، لا سيما لدى المرضى الذين يعانون من أورام دموية، حيث يمكن أن يؤدي التشخيص الخاطئ إلى علاج غير كافٍ ونتائج سيئة للمرضى.

المنهجية :تستعرض هذه المراجعة دراسات الحالات والأدبيات الحديثة لاستكشاف التداخل السريري بين نقص المناعة الأولي والثانوي والأورام الدموية. تم إجراء بحث شامل في قواعد البيانات الوطنية والإرشادات السريرية لتحليل أنماط التشخيص، استراتيجيات العلاج، وآثار نقص المناعة على تشخيص السرطان.

النتائج :تشير النتائج إلى أن نسبة كبيرة من المرضى المصابين بالأورام الدموية يظهرون أيضًا علامات نقص المناعة، مما يزيد من تعقيد التشخيص. تسلط دراسات الحالات الضوء على أمثلة حيث يخفي نقص المناعة الثانوي نقص المناعة الأولي، خصوصًا لدى المرضى الذين عُولجوا بعلاجات مثبطة للمناعة مثل ريتوكسيماب. تؤكد المراجعة على أهمية التقييم المناعي المبكر للمرضى الذين يعانون من عدوى متكررة وأورام خبيثة.

الاستنتاج :يُعد التمييز بين نقص المناعة الأولي والثانوي أمرًا ضروريًا لتحسين إدارة المرضى والتدخلات العلاجية. يتطلب التعرف المبكر على نقص المناعة الأولي زيادة الوعي واعتماد نهج متعدد التخصصات، خاصة لدى المرضى الذين يعانون من أورام دموية. ينبغي أن تركز الأبحاث المستقبلية على تطوير بروتوكولات فحص موحدة لنقص المناعة في سياقات الأورام لتحسين نتائج المرضى.

الكلمات المفتاحية :نقص المناعة الأولي، نقص المناعة الثانوي، الأورام الدموية، التقييم المناعي، تشخيص السرطان.