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Multifocal Tuberculosis in an Immunocompetent Patient Revealing Polyclonal Dysgammaglobulinemia; Leading Us to Consider a Primary Humoral Immunodeficiency in Adults, Either Selective IgG Deficiency or Atypical Onset Common Variable Immunodeficiency

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Abstract **Case Report**

Immunoglobulin G subclass deficiency (IgGSCD) is a relatively common primary immunodeficiency disease (PI) in adults. We report the case of a 52-year-old patient admitted to the medical ward of the Point G University Hospital in Bamako, Mali, for chronic cough and prolonged fever. Following a clinical examination and meticulous diagnostic workup, we diagnosed in an immunocompetent HIV patient, multifocal tuberculosis with polyclonal dysgammaglobulinemia, suggesting a primary immunodeficiency, either selective IgG deficiency or early atypical common variable immunodeficiency.

Keywords: Primary Humoral Immunodeficiency, Selective IgG deficiency, Common Variable Immunodeficiency, Internal Medicine.

INTRODUCTION

Immunodeficiency, defined as a weakened or dysfunctional immune system that increases susceptibility to infections and cancer, is common in adults. Recent estimates suggest that more than 6% of US adults may be affected [1], with most cases resulting from secondary immunodeficiencies (SID). These deficiencies arise due to external factors such as human immunodeficiency virus (HIV) infection, medications, intrinsic factors including systemic diseases, malignancies, and metabolic disorders, or a combination of both. Primary immunodeficiencies, traditionally referred to as "primary immune deficiencies (PIDs)," are now classified as inborn errors of immunity (IEI).

These primary immunodeficiencies comprise at least 200 inherited diseases that are thought to be individually and collectively rare [1]. The exact prevalence and incidence of PIDs remain uncertain, but recent epidemiological studies have suggested that PIDs are much more common than generally believed. Underdiagnosis of this condition is thought to be due to a lack of awareness of PIDs, their highly heterogeneous clinical presentation, and the often perceived difficulty of their investigation. Among these primary immunodeficiencies, humoral immunodeficiencies (HIDs) are by far the most common [1]. In contrast to the majority of primary immunodeficiencies involving other components of the immune system, HIDs can manifest at any age, with peaks in childhood and the third decade of life [1].

Their common end result is the inability to mount an effective immune response against invasive pathogens [2]. Defective antibody production leads to recurrent and/or severe infections. ILDs present with a heterogeneous spectrum of clinical symptoms, most

often ranging from asymptomatic forms in selective IgA and IgG subclass deficiencies; to common variable immunodeficiency (CVID); to severe congenital agammaglobulinemias in which the production of all immunoglobulin isotypes is severely reduced [2].

In Africa, up to 902,631 people may have a PIDs, while only 1,016 cases are currently registered in the African registry [3]. Currently, in Morocco, more than 400 cases are listed in the Moroccan PIDs registry, but it appears that the number of patients with this disease in Morocco is at least five times this figure [3]. We do not have recent published clinical case data concerning PIDs in Mali, hence this article.

We report the case of an immunocompetent adult patient with multifocal tuberculosis diagnosed in the Internal Medicine department of the Point G University Hospital in Bamako who, during the etiological investigation, revealed a polyclonal dysgammaglobulinemia; leading us to consider a primary humoral immunodeficiency in the adult, either a selective IgG deficiency or an early atypical common variable immunodeficiency.

OBSERVATION

We report the case of a 52-year-old male patient, a Malian merchant. She was admitted on March 9, 2026, to the internal medicine department of the Point G University Hospital Center in Bamako for a chronic cough and persistent fever.

The symptoms began approximately four months prior, characterized by a progressively worsening productive cough with whitish sputum not streaked with blood. This cough was persistent, without chest pain, and accompanied by dyspnea (NYHA class II). The fever, which developed concurrently with the cough, was not quantified, and occurred in the evenings and at night with excessive sweating. This symptomatology was followed by several episodes of altered consciousness characterized by incoherent speech and disorientation, with blurred vision, no history of trauma, no headaches, and projectile vomiting. The patient also reported frequent urination, requiring him to get up three times a night to urinate, without any associated burning sensation during urination. All of this is occurring within the context of significant, unquantified weight loss, physical asthenia rated at 6/10 according to the ENG scale, anorexia on solid food, and agesia. Given the persistence of these symptoms, his family decided to consult us for treatment. History of cataractectomy in 2025, both his parents are diabetic and hypertensive, one sister is diabetic. He reportedly took bromazepam and vitamin D3; the indications and dosages were not specified.

The general examination revealed a conscious, emaciated patient with conjunctival pallor; afebrile on touch; her Karnofsky performance status was 70%. Her left arm blood pressure, in the seated position, was 110/77 mmHg; her heart rate was 144 bpm; her respiratory rate was 42 breaths per minute; her left axillary temperature was 37.7 °C; her capillary blood glucose on admission was 0.98 g/L. Her measurements on admission were as follows: weight 63 kg, height 168 cm, with a body mass index (BMI) of 22.32 kg/m²; SpO2 91%. The anamnesis and the meticulous physical examination allowed us to identify a bacillary impregnation syndrome consisting of evening-night fever, asthenia, anorexia, and weight loss; a pulmonary consolidation syndrome consisting of increased vocal fremitus and crackling rales in both hemithorax associated with a decrease in breath sounds; a febrile syndrome consisting of low-grade fever, tachycardia, and polypnea; and a tumor syndrome consisting of a painless left testicular swelling measuring 14 cm long and 12 cm wide.

The paraclinical assessment showed:

Hemogram: Hypochromic microcytic anemia with a hemoglobin level of 10.2 g/dL, the mean corpuscular volume (MCV) of 75.3 fl; a CCMH at 31.2 g/dL. Normal leukocyte count (6500/mm^3) but with lymphopenia at 810/mm^3; a complete lymphocyte count was requested but not performed, as surface lymphocyte markers are not feasible in our setting

Inflammatory Assessment: An inflammatory syndrome with a CRP of 54.81 mg/L. VS at 87mm at the 1st hour and at 121mm at the 2nd hour. Ferritinemie at 756.75ng/mL Serum protein electrophoresis revealed hypoalbuminemia (45.7g/L), Hyperalphaglobulinemia 1 and 2; albumin/globulin ratio at 0.89. A mixed gamma globulin abnormality was observed, revealing total hypergammaglobulinemia (19.2 g/L) with an unbalanced dysgammaglobulinemic profile on quantitative immunoglobulin testing, with hyper-IgA at 9.37 g/L (0.7–4.0) and hypo-IgG at 6.24 g/L (7.00–16.00). Gamma globulin immunofixation showed a polyclonal IgG profile (Picture 1) with low IgG2 and IgG4 levels.

Infectious Assessment: Negative HbsAg, anti-Hbc Ab IgG positive, anti Hbs Ac negative, HIV1-2 and HCV serologies are negative. Negative thick drop. The search for Mycobacterium tuberculosis using the Xpert gene on sputum examination was positive, with no resistance to rifampicin.

Biochemical Assessment: Serum creatinine at 136.8 µmol/l with clearance at 59 ml/min/m^2. Azotaemia at 9.8 mmol/L. Hypocalcemia at 2.11 mmol/L, Hypomagnesiema at 0.66 mmol/L, natremia at 130mmol/L, kalémia at 3.6 mmol/L. Total protein at 76.0 g/L, 24-hour proteinuria at 0.36g/24h. Adenosine deaminase elevated at 23.4 U/l. Fasting blood glucose and HbA1c levels are normal. A 24-hour proteinuria test and urine protein electrophoresis were normal. Purine Nucleoside Phosphorylase (PNP) assay was requested

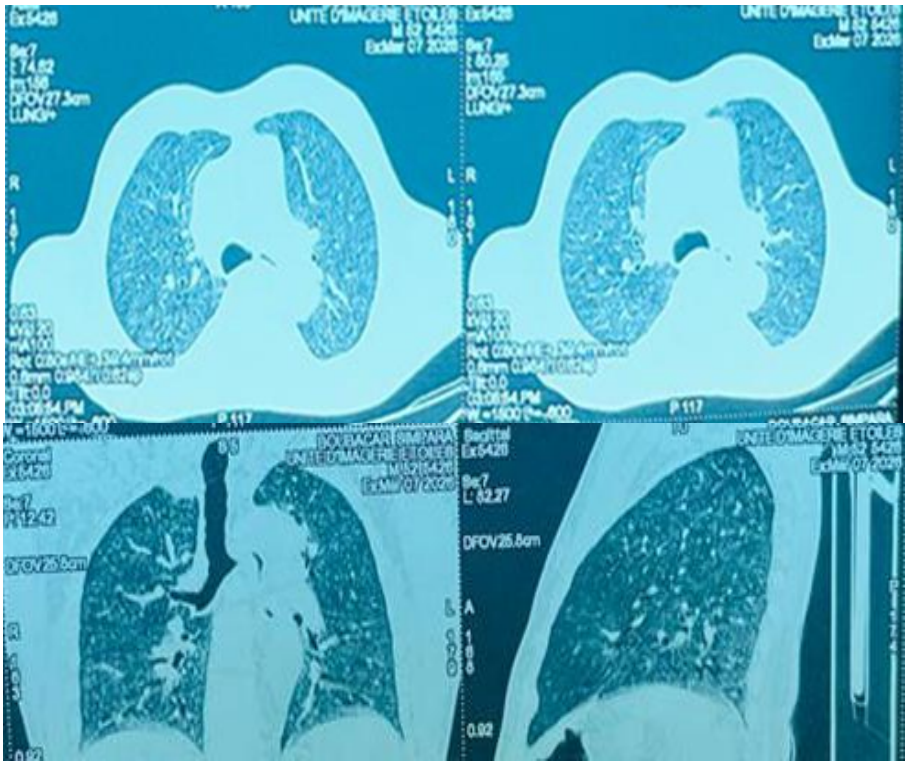
but not feasible in our setting. Fecal calprotectin was requested but not performed.

Immunological Assessment: Anti-nuclear antibodies (ANA-Screen) at 0.18 (negative), anti-native DNA at 10.00 ui/mL (negative). Cryoglobulin assay was negative. Lymphocyte immunophenotyping to quantify and characterize the different subpopulations of lymphocytes (B, T, and NK) in the blood was requested but not performed. Complement dosage showed global hypercomplementemia CH50 > 60U/ml, C3 at 2.03 g/L and C4 at 0.45 g/L.

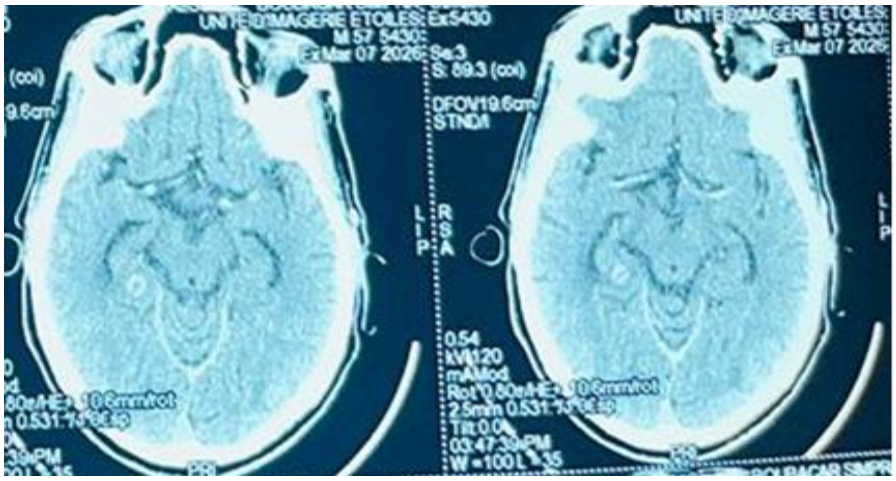
Molecular biology test: The search for mutations in the GATA2 gene is not feasible in our environment.

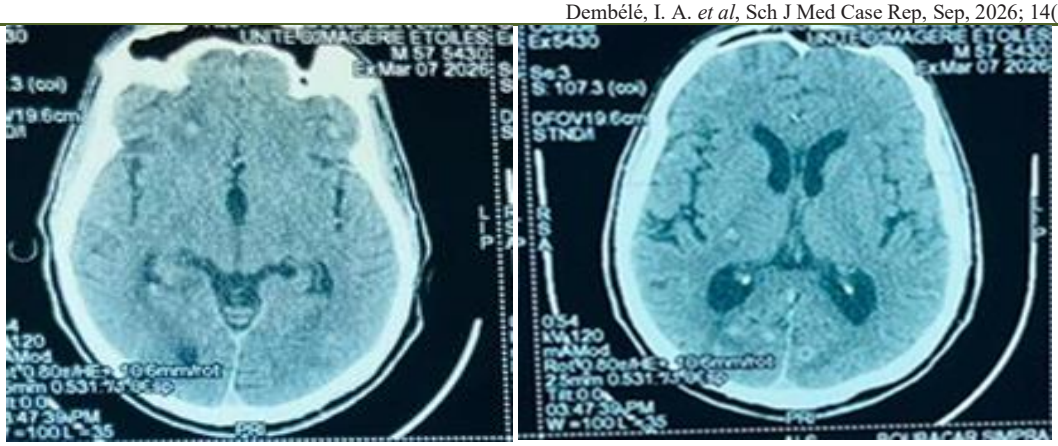
In terms of imaging:

- Testicular ultrasound was consistent with a left testicular expansive process associated with a reactive hydrocele.
- The chest scan reveals miliary tuberculosis with micronodules of hematogenous distribution, disseminated throughout both lung fields, giving the classic "millet grain" appearance. (Picture 1)
- The brain scan reveals miliary tuberculosis, the presence of multiple intra-axial nodular formations with peripheral enhancement after contrast injection, and supra- and infratentorial dissemination associated with perilesional hypodensities. (Picture 2)



Picture 1: Chest CT scan without contrast injection, axial, coronal and sagittal slices, parenchymal windows showing multiple disseminated pulmonary micronodules





Picture 2: The patient's axial brain scan, showing multiple intra-axial nodular formations and supra- and infratentorial dissemination associated with perilesional hypodensities

These clinical, radiological, and immunological arguments led us to consider and retain the following as the main diagnostic a primary humoral immunodeficiency in adults: selective IgG deficiency disease or an atypical onset common variable immunodeficiency revealed by multifocal tuberculosis (encephalic, pulmonary and testicular) in an immunocompetent patient; according to the European Society for Immune Deficiencies (2015).

The patient was started on antituberculosis therapy (combined with pyridoxine) according to the recommendations of the country's National Tuberculosis Control Program. The regimen consisted of rifampicin (10 mg/kg/day), isoniazid (5 mg/kg/day), pyrazinamide (25 mg/kg/day), and ethambutol (15 mg/kg/day) at fixed doses based on the patient's weight, i.e., four tablets per day for the first two months. This was followed by dual therapy (rifampicin 10 mg/kg/day and isoniazid 5 mg/kg/day) at fixed doses based on the patient's weight, i.e., four tablets per day for 10 months. A brief course of oral corticosteroid therapy was initiated by administering prednisone at a dosage of 1 mg/kg/day (i.e., 60 mg/day) for one month in association with adjuvant measures, followed by a gradual taper until complete cessation; this was to minimize signs of encephalitis and to prevent post-miliary pulmonary fibrosis; rehydration, anticoagulant prophylaxis with enoxaparin and a high-calorie diet.

After a 15-day hospital stay, the patient returned home with follow-up appointments at the Internal Medicine Department of the Point G University Hospital in Bamako. These clinical and bacteriological check-ups allowed for monitoring of the therapeutic progress. Bacteriological monitoring was performed two months into the antituberculosis treatment. The clinical and biological progress was favorable, both in the short and long term. Indeed, it was marked by clinical improvement with a resolution of the symptoms of tuberculosis infection, pulmonary consolidation syndrome, and fever; weight gain; and the disappearance of headaches. However, a non-transluminescent left scrotal swelling persisted, and sputum smears for tuberculosis became negative on the second-month follow-up. Nevertheless, the biological inflammatory syndrome persisted (CRP at 14.80 mg/L). An immunological test (quantitative measurement of immunoglobulins) was requested but not performed. The application of the directly observed treatment (DOT) strategy demonstrated good adherence and medication tolerance throughout the treatment in our patient. Drug tolerance was monitored by checking for major and minor adverse effects at each contact.

DISCUSSION

This observation reports a case of primary humoral immunodeficiency in an adult; either a selective IgG deficiency disease or an early atypical common variable immunodeficiency revealed by multifocal tuberculosis (brain, lung and testicular) in an immunocompetent patient; according to the European Society for Immunodeficiency Diseases (2015). PIDs have traditionally been viewed as a group of illnesses that occur in pediatric patients. New advances in diagnosis and treatment have led to an increase in adult PID patients. Studies performed in the past decade have provided evidence that the prevalence of PIDs in adults has been underestimated [2]. Data from the United States Immunodeficiency Network (USIDNET) registry demonstrate that 16.7% of PID patients are enrolled before 18 years of age; however, 83.3% are enrolled after 18, and 14.0% are enrolled after 65 [2]. The latest data from the European Society for Immunodeficiencies (ESID) registry demonstrate that 9% of all subjects present with initial manifestations after 40 [2]. Global data from the Jeffrey Modell Foundation (JMF) demonstrated that the proportion of the adult population with PIDs increases over time [2].

Yount et al; in the 1960s and Schur et al, in the early 1970s described patients with imbalances in their IgG subclasses and recurrent sinopulmonary infections [6]. Despite the availability of highly specific antisera and more sensitive assays, the clinical significance of low serum IgG subclass levels observed in the laboratory

remains controversial [3,5]. Healthy individuals without recurrent infections can have low serum IgG subclass levels; clinical immunologists debate whether IgG subclass deficiency represents true immunodeficiency [6].

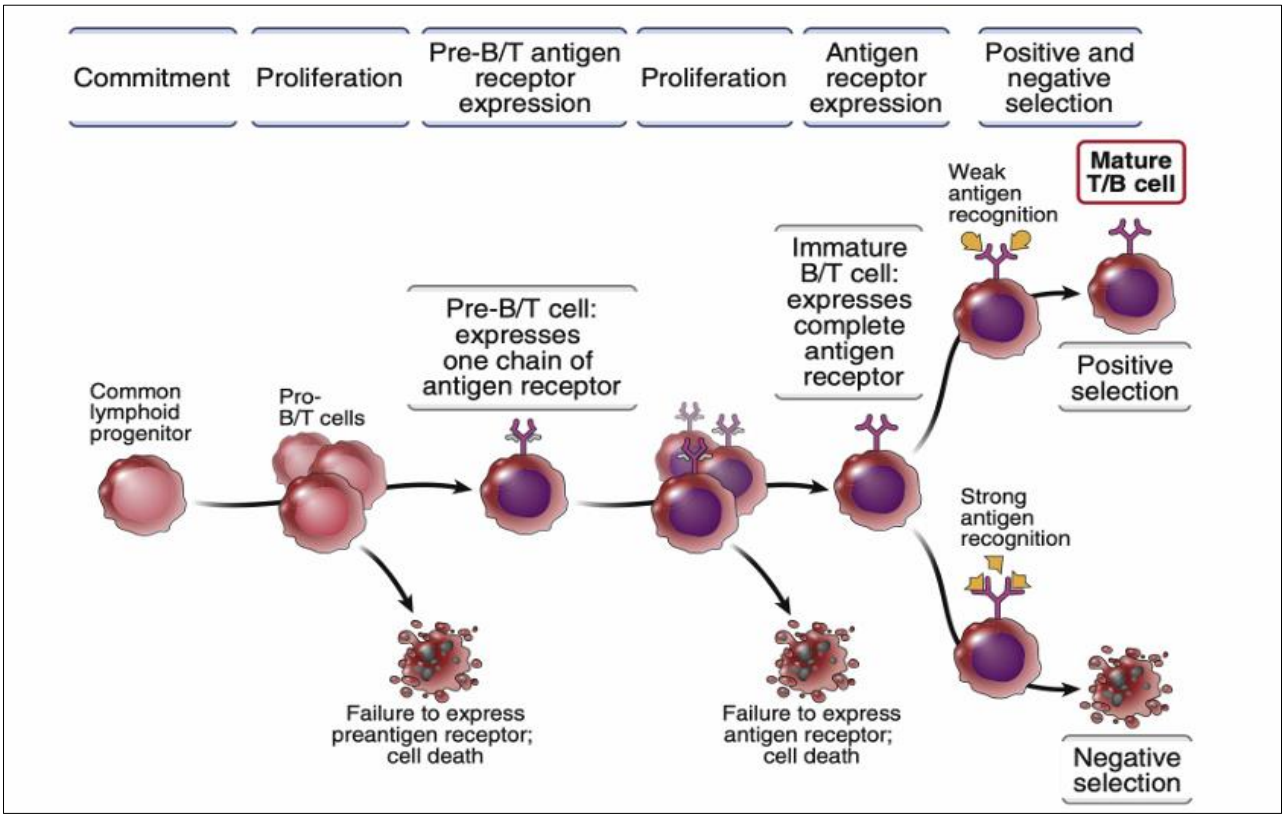
➢ **Développement et maturation des lymphocytes B**

Immunoglobulins (Ig) are secreted by plasma cells, which represent the final stage of B lymphocyte differentiation. B lymphocytes develop from hematopoietic stem cells (lymphoid precursors) in the bone marrow, where they undergo a series of differentiations during which the genes of the B cell receptor (BCR) are rearrangemented. These BCRs are represented by a signaling complex associated with a membrane-bound IgM molecule. These BCRs are capable of recognizing a wide variety of antigens. The successful expression of the first heavy chain (Mu) and subsequently the light chain (Kappa or Lambda) on the surface of the immature B cell allows the continuation of differentiation from the pre-B stage to the naïve mature B cell stage. This cell leaves the bone marrow and joins the pool of circulating B lymphocytes. These events are summarized in Figure 1 [3,5].

After leaving the bone marrow, the encounter of the B lymphocyte with the antigen in the regional lymph nodes initiates a further series of B lymphocyte differentiations, culminating in the production of immunoglobulins. Indeed, following the interaction between the B lymphocyte and the antigen-specific T lymphocyte, isotype switching leads to the substitution of the initial IgM by high-affinity IgG, IgA, or IgE. The fundamental initial role of IgM lies in binding to intravascular pathogens and in complement activation, while the secondary immune response, characterized by the production of IgG, IgA, and IgE immunoglobulins, is necessary for continuous and effective protection against invasive pathogens [3,5].

IgA performs multiple functions in mucosal defense. In the extravascular environment, IgG is the key effector in the opsonization and complement activation processes. IgE is involved in defense against parasites. The production of high-affinity IgG is a cornerstone of successful vaccination and a key component of immunological memory against various infectious agents. Disorders resulting from a deficiency in each of the aforementioned steps have varying degrees of clinical severity [3,5].

Polysaccharide antigens, present in the cell wall of encapsulated bacteria such as pneumococci and meningococci, induce a T-independent antibody response that occurs in the marginal zone of the spleen. The T-independent B-cell response is immature in healthy children under 2 years of age, hence their vulnerability to serious complications from pneumococcal and meningococcal infections [5].



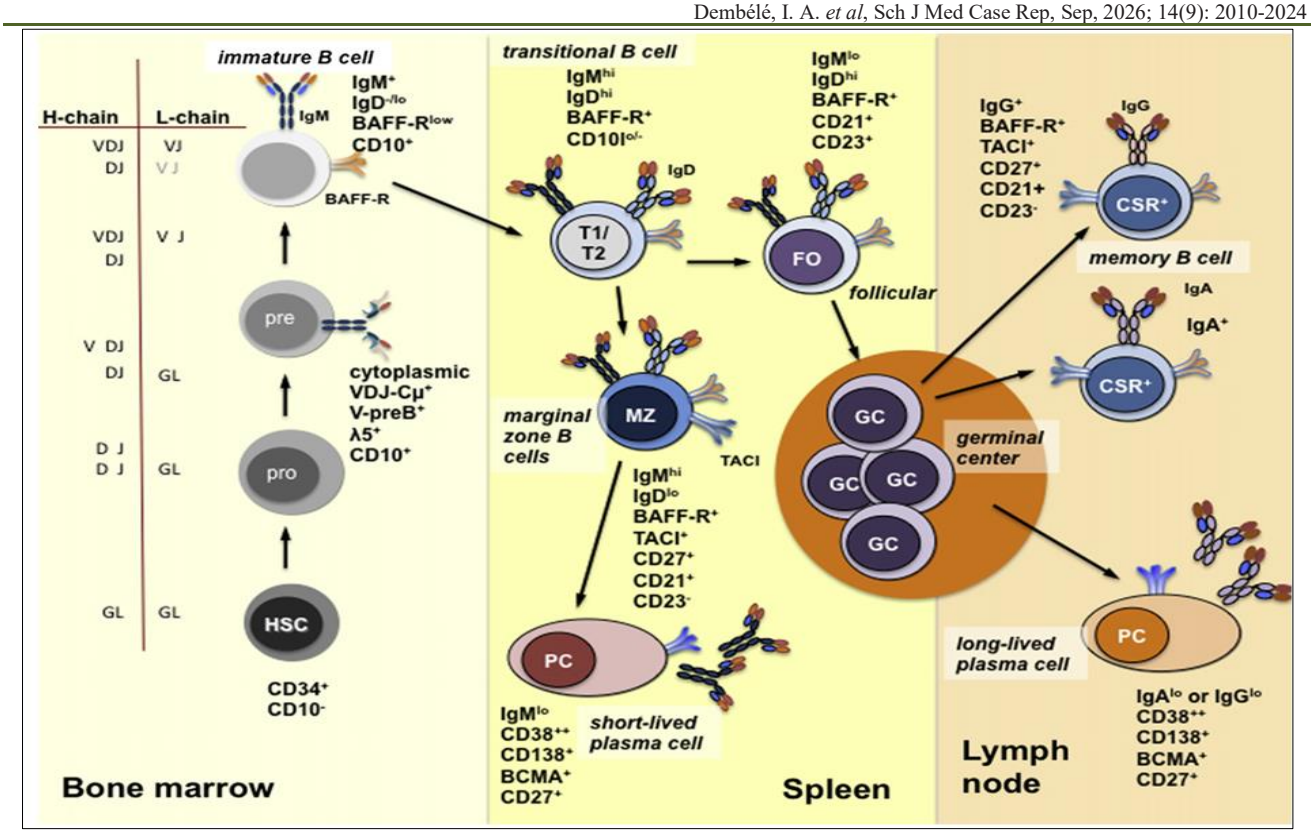


Figure 1: B-cell development and B-cell subsets. B cells develop in the BM from hematopoietic precursor cells (HSC)

➢ **Types of Immunodeficiency**

- **Primary Immunodeficiency**

Distinguishing between IEI and SID in adult patients can be challenging, as autoimmune and hematologic or oncologic conditions can be both the causes and the manifestations of immune dysfunction. IEI is usually diagnosed during child hood, but some entities, particularly CVID, may manifest in adulthood. In addition, hypomorphic variants of clas sically severe IEI (e.g., mutations in RAG1/2, ADA2, or NF-κB1 genes) can present with attenuated phenotypes and be diagnosed later in life [14]. CVID is defined by reduced levels of immunoglobulins G (IgG) along with low levels of IgA and/or IgM, defective responses to immunizations, and abnormal B cell immunophenotype, often with significant reduction of isotype-switched memory B cells [15]. CVID represents a heterogenous group of disorders with variable clinical phenotypes, contributing to delayed diagnosis. Most patients are diagnosed between 20 and 45 years of age after multiple consultations and hospitalizations [16]. While genetic variants are identified in 25–30% of cases, novel disease-causing mutations continue to be discovered [17]. The clinical presentation and potential complications can vary according to the underlying genetic defect.

The main clinical feature of CVID is recurrent respira tory tract infections, such as pneumonia, sinusitis, and otitis media, mainly due to Streptococcus pneumoniae and Hae mophilus influenzae, which have been reported in over 90% of patients in large studies [16]. Viral (e.g., herpes zoster), fungal (e.g., Pneumocystis jirovecii), and parasitic (e.g., Giardia) infections are less frequent [16]. In adults with recurrent respiratory infections, the presence of allergy, autoimmunity, and/or granulomatous disease should raise the suspicion of underlying CVID [18]. Patients with pre dominant non-infectious complications (autoimmunity, lymphoproliferation, enteropathy) are increasingly recog nized as a distinct subgroup of CVID with different patho physiology and outcomes compared to those with mainly infectious manifestations [19]. Additional complications affecting CVID patients include atopy, immune thrombo cytopenic purpura, hemolytic anemia, lymphoproliferation, splenomegaly, protein-losing enteropathy, and granuloma tous lymphocytic interstitial lung disease (GLILD) [20]. Bronchiectasis and interstitial lung disease are major com plications of pulmonary infections and represent key signs for CVID diagnosis.

- **Secondary Immunodeficiency**

SID conditions are acquired, tend to appear later in life, and can be transient or permanent. They result from external factors that impair immune function. Identifying the under lying cause is crucial, as targeted interventions can often alleviate or reverse immune dysfunction.

SID Inducing Drugs

Medications represent one of the most frequent causes of SID in adults. Various drug classes can impair the immune system, including cytotoxic agents, glucocorticoids, tradi tional immunosuppressants, biological and targeted thera pies, and cellular therapies, as well as certain antiepileptic and antipsychotic drugs (Table 2). A comprehensive review of current and past medication history is crucial for the rec ognition of drug-induced immunosuppression.

Glucocorticoids exert anti-inflammatory and immunosup pressive effects in a dose and duration-dependent manner [31], and may lead to hypogammaglobulinemia and CD4 lymphopenia [22, 32]. Similarly, biological agents used to treat autoimmune disorders and malignancies increase the risk of infection through mechanisms specific to their targets and off-target enzyme inhibitions. For example, anti-CD20 monoclonal antibodies, such as rituximab, cause prolonged B-cell depletion, while hypogammaglobulinemia can also occur, especially with prolonged courses [33]. Some patients also develop late-onset neutropenia, which is believed to result from immune dysregulation, including cytokine imbalance that impairs neutrophil production [34]. Impaired vaccine responses, severe respiratory infections, reactiva tion of hepatitis B virus, and even progressive multifocal leukoencephalopathy (PML) in rare cases are reported [33]. Tumor necrosis factor alpha (TNF-α) inhibitors are consist ently associated with an increased risk of tuberculosis and potentially a higher risk of serious infections, particularly early in treatment, as well as with reactivation of hepatitis B infection [25].

Of note, immunosuppressive drugs are often used in com bination, leading to an increased immunosuppressive state. For example, combined drug regimens used after solid organ transplantation (SOT) to avoid transplant rejection often include glucocorticoids, calcineurin inhibitors, lymphocyte proliferation inhibitors and/or mechanistic target of rapa mycin (mTOR) inhibitors, while anti-thymocyte globulins (ATG) and anti-IL-2 receptor antibodies are also frequently used at induction. These agents are known to cause profound immunosuppression, especially of the cell-mediated immu nity and lead to a high infection risk after SOT [35]. The list of biological and targeted molecules with immu nosuppressive potential is rapidly expanding, reflecting the continuous development of novel agents in oncology, auto immunity, and transplantation. It is increasingly challeng ing for non-specialists to remain familiar with their diverse mechanisms of action and infectious risks. For this reason, updated consensus documents, such as those from the ESC MID Study Group for Infections in Compromised Hosts (ESGICH), are valuable resources that provide comprehen sive, regularly revised guidance on infection risk stratifica tion and management [36].

Metabolic Causes

Diabetes mellitus is the most common metabolic disorder associated with immune dysfunction, leading to an increased susceptibility to infections [37]. Chronic hyperglycemia impairs both innate and adaptive immunity, affecting neu trophil chemotaxis, phagocytosis, and cytokine responses. Obesity without diabetes is also associated with autoimmun ity and immune dysfunction, suggesting a causal relation ship [38]. Patients with Cushing's disease are at a higher risk of infection due to increased endogenous glucocorticoid production, which suppresses inflammatory and immune responses [39]. To a lesser extent, thyroid dysfunction can contribute to weakening immune function due to its effect on T-cell function. Other hormonal dysfunctions that can impact the immune system include hypopituitarism, adrenal insufficiency, growth hormone deficiency, and imbalances in sex hormones.

Infectious Causes

Chronic infections can contribute to SID by directly target ing immune cells or inducing prolonged immune activation and exhaustion. HIV is the most well-known infectious cause. In the absence of antiretroviral therapy, HIV infection progressively leads to CD4 + T-cell depletion and impaired cell-mediated immunity, increasing vulnerability to encap sulated bacteria (S. pneumoniae) and severe opportunistic infections including viral (reactivation of herpesviruses, JC virus), fungal (including Pneumocystis jirovecii, Cryptococ cus spp, Candida spp), parasitic (toxoplasmosis), and myco bacterial pathogens. Infection risk is strongly correlated with CD4 T-cells counts. HIV also disrupts innate immunity, impairing alveolar macrophage function, reducing neutrophil and NK cell activity, and altering B-cell responses, leading to defective antibody production and poor vaccine induced immunity [40, 41]. Additionally, chronic immune activation and gut barrier disruption contribute to systemic immune dysfunction.

Protein Loss

Protein-losing conditions can lead to hypogammaglobu linemia due to excessive immunoglobulin loss that is not adequately compensated by synthesis. In nephrotic syn dromes, proteins including immunoglobulins are lost in the urine, with hypogammaglobulinemia further exacerbated by impaired IgG synthesis and by the use of B-cell-targeting medications [42, 43]. Protein-losing enteropathy (PLE) results from excessive protein loss through the gastrointes tinal tract and can complicate various conditions, including inflammatory bowel disease, systemic lupus erythematosus, coeliac disease, graft versus host disease, bacterial over growth, and intestinal infections such as viral or parasitic enteritis and Whipple disease. PLE may also be associated with cardiovascular disorders and neoplasms [44]. Addition ally, PLE can occur as a complication of IEI, such as CVID, further exacerbating hypogammaglobulinemia.

Lymphatic Malformations and Primary Intestinal Lymphangiectasia

Lymphatic malformations and primary intestinal lymphan giectasia (PIL) are rare but significant causes of SID. These conditions are characterized by abnormal development or dysfunction of lymphatic vessels, leading to excessive loss of lymphatic fluid rich in proteins, lymphocytes, and immunoglobulins [45, 46]. As a result, affected individuals often develop hypogammaglobulinemia, lymphopenia, and impaired humoral and cellular immune responses, increas ing their susceptibility to infections. Clinically, it manifests with peripheral edema, chylous ascites, chronic diarrhea, and recurrent infections, particularly with encapsulated bac teria [47]. Patients with PIL may also present with profound and selective lymphopenia, further compromising immune defenses [48]. Generalized lymphatic malformations, as seen in certain congenital syndromes (e.g. Hennekam syndrome), can also lead to SID due to systemic lymphatic leakage [49, 50].

Hematological Malignancies

Patients with hematological malignancies have a high infec tious risk due to the underlying malignancies and treat ments. Infectious risk is highest in those with acute leuke mia receiving induction and consolidation chemotherapies resulting in prolonged neutropenia (> 10 days), and in recipients of allogeneic hematopoietic cell transplantation (HCT), especially in the context of additional immunosup pression for prevention or management of graft versus host disease (GVHD) [51, 52]. Novel cellular therapies such as chimeric-antigen-receptor (CAR) T-cell therapies are increasingly used in B-cell and plasma cell malignancies and lead to profound and persistent immune deficits in cel lular and humoral immunity [53]. Importantly, emerging treatments—including bispecific T-cell engagers and CAR T-cell therapies—further underscore the need for heightened vigilance in assessing infection risk. The duration of neutro penia is a key determinant of infection risk in these “high risk” patients with hematological malignancies, increasing risk for bacterial and fungal infection and dictating preven tive strategies. Cellular immunodeficiency after allogeneic HCT increases the risk of herpesvirus infection, especially cytomegalovirus (CMV), that requires special prophylactic strategies in this setting. Finally, humoral immune deficits are also frequent, both after HCT and CAR T-cell therapies (“on-target off-tumor effects”), and lead to frequent sinopul monary infections. Other hematological malignancies, such as myeloma and lymphoma, can lead to immunodeficiencies through multi ple mechanisms [54]. Multiple myeloma disrupts normal antibody production through the expansion of clonal plasma cells that produce large quantities of dysfunctional mono clonal immunoglobulins, while simultaneously suppressing normal immunoglobulin synthesis. In lymphoma, immune dysfunction arises due to bone marrow involvement, chemo therapy-induced myelosuppression, and direct impairment of B- and T-cell function. Patients with these malignancies are at increased risk for recurrent bacterial infections, particu larly with encapsulated organisms, due to impaired humoral immunity.

Hypogammaglobulinemia is frequent in patients with chronic lymphocytic leukemia (CLL) due to the progressive loss of normal B-cell function, leading to impaired immuno globulin production and defective humoral immunity [55]. The severity of B-cell dysfunction correlates with disease progression and treatment exposure, particularly with anti CD20 monoclonal antibodies and Bruton tyrosine kinase (BTK) inhibitors, which further deplete B-cell populations.

Thymoma can also be associated with B-cell lymphope nia and hypogammaglobulinemia, leading to a rare form of secondary immunodeficiency known as Good’s syndrome [56]. The immune defect in Good’s syndrome extends beyond B-cell deficiency and may include T-cell abnormali ties, resulting in susceptibility to both bacterial and oppor tunistic infections.

Malnutrition and Aging

Malnutrition is a leading cause of SID worldwide and affects both children and adults, particularly in low-income countries. Chronic caloric and protein deficiencies impair immune cell development, proliferation, and function, increasing susceptibility to infections. Micronutrient defi ciencies, including zinc, vitamin A, vitamin D, iron, and selenium, weaken mucosal barriers, and impair innate and adaptive immune responses [57]. Hypoproteinemia results in decreased T cell generation and function, with immunosup pression correlating with the severity of protein depletion [58].

Immunosenescence, the gradual decline of immune func tion with age, results in reduced naïve T-cell production, impaired B-cell responses, and diminished innate immune activity. Elderly individuals experience weakened vac cine responses, increased susceptibility to infections, and a higher prevalence of chronic inflammation (“inflammag ing”), which contributes to immune dysregulation [57]. These age-related changes along with a higher burden of comorbidities make older individuals particularly vulnerable to pneumonia, influenza, and other infectious diseases, often with more severe outcomes.

Other Causes

Chronic kidney disease (CKD) and liver cirrhosis can also lead to SID by multiple mechanisms. In CKD, uremic tox ins impair neutrophil chemotaxis, phagocytosis and oxida tive burst, reducing innate immune defenses and increas ing susceptibility to bacterial infections [59]. Furthermore, CKD leads to T-cell dysfunction, with decreased activation, proliferation, and cytokine production, further compromis ing adaptive

immunity [60]. Liver cirrhosis results in the dysfunction of Kupffer cells, the resident macrophages of the liver, resulting in impaired pathogen clearance and endo toxin tolerance. Additionally, it is associated with decreased acute-phase reactant production, impaired neutrophil func tion, and complement deficiency, all of which contribute to the increased risk of spontaneous bacterial peritonitis and systemic infections [61].

Other causes of SID include splenectomy, functional hyposplenia or asplenia, thymectomy, radiation therapy, and plasmapheresis. Splenectomy results in impaired clearance of encapsulated bacteria, predisposing individuals to over whelming post-splenectomy infections syndrome (OPSI) [62]. Functional hyposplenia, as found in sickle cell disease patients, alters immunophenotype and also predisposes to bacterial infections [63]. Thymectomy, particularly when performed early in life, can significantly reduce T-cell out put, leading to a weakened adaptive immune response [64]. Radiation therapy, especially when targeting the bone mar row or lymphoid tissues, leads to lymphopenia and neutro penia, increasing the risk of infections [65]. Plasmapheresis, used to remove pathogenic antibodies, can also deplete pro tective immunoglobulins [66]

- **Immunopathology of primary humoral deficiencies in adults**

A defect occurring during critical stages of B cell development has the potential to cause DIH (Figure 1), but the immunological and genetic defects in most patients with DIH are still unknown [12]. Depending on the nature of the B cell defect, DIH can be separated into different categories, each with its own clinical, immunological, and genetic characteristics.

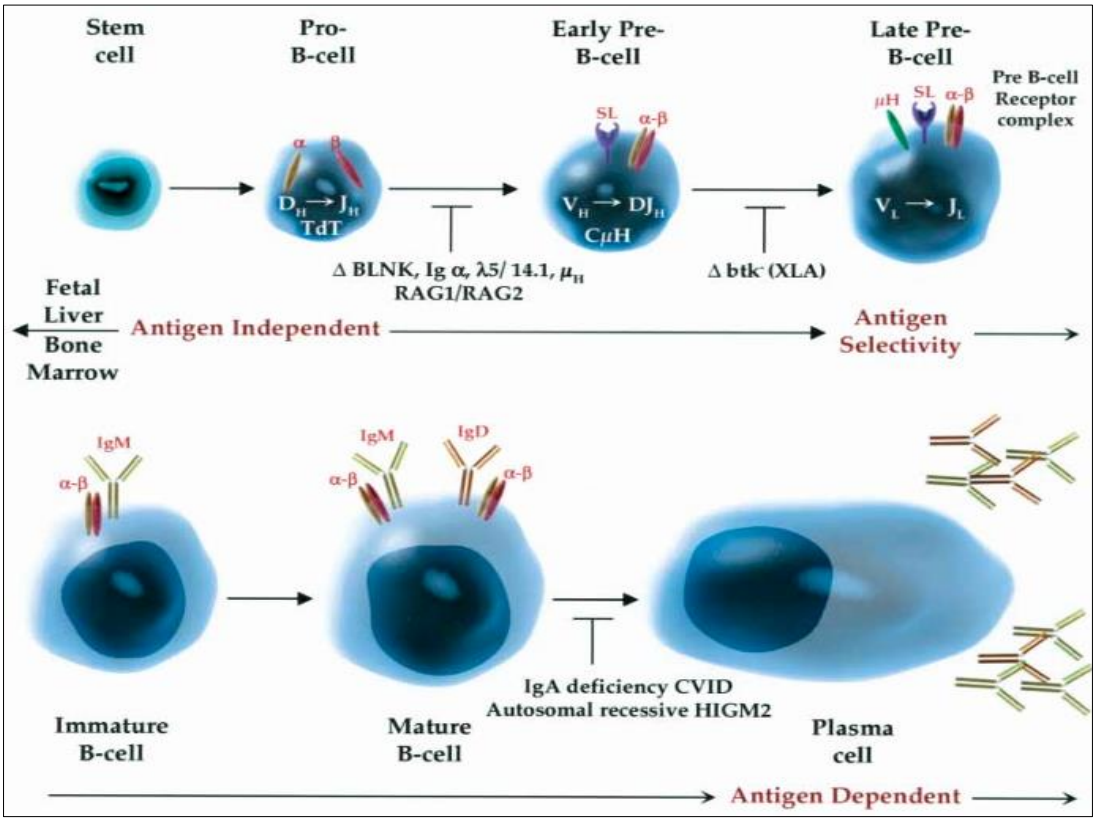


Figure 2: B-cell development and the mutations that lead to antibody deficiencies [6]

Common variable immunodeficiency (CVID)

Common variable immunodeficiency (CVID) is an idiopathic immunodeficiency with an estimated prevalence of 1/25,000 [5]. It is defined by serum IgG levels below 2 standard deviations from normal in the presence of decreased IgA and/or IgM, recurrent infections, impaired response to vaccination, exclusion of previously defined causes of hypogammaglobulinemia, and an age greater than 2 years [32]. A considerable group of patients suffer from a similar idiopathic hypogammaglobulinemia but do not meet all the diagnostic criteria. These patients are usually diagnosed as "possible" CVID or as having a "CVID-like" disorder. Their clinical features are indistinguishable from those of CVID.

The reported abnormalities involved include impaired B-cell activation (CD19 [33] and CD81 [34] deficiencies), impaired co-stimulation (ICOS [35] abnormality), and impaired B-cell survival (BAFF-R [36] deficiency). In addition, other genetic abnormalities have been identified, but these do not cause true hypogammaglobulinemia but simply an increased susceptibility to disease (TACI deficiency). The

heterogeneity of the immunological manifestations and the fact that many cases likely go undetected because they are clinically indicative of CVID hinder the discovery of the underlying disease mechanisms, prognostic factors, and genetic abnormalities.

Most CVID patients are diagnosed in young adulthood, but symptoms appear in childhood in more than half of cases [4]. Consequently, a diagnostic delay of more than 5 years is the norm [6, 42]. Sometimes CVID is preceded by a deficiency in IgA, an IgG subclass, or a deficiency in specific anti-polysaccharide antibodies. The symptoms of CVID are diverse, but recurrent respiratory and ENT infections are present in more than 90% of patients. Some patients have an autoimmune disease, most often an autoimmune cytopenia. Other clinical manifestations include granulomatous inflammation of the lungs and gastrointestinal tract, unexplained chronic diarrhea, and hematological cancers, which are significant causes of death. Patients with CVID who experience at least one non-infectious complication have a higher mortality rate than patients who only experience infectious complications [43].

Selective antibody deficiency: IgG

There is increasing evidence that IgG subclasses play a crucial role in preventing viral or bacterial infections. IgG1 is the most prevalent subclass, comprising up to 70% of the total IgG level; therefore, a lack of IgG1 in patients with various primary and secondary antibody deficiencies can decrease total IgG levels (hypogammaglobulinemia). IgG1 deficiencies, sometimes in combination with other IGGSCDs, are associated with recurrent infections. IgG2 subclass deficiency predisposes patients to infections due to an inability to generate measurable titers of antibodies to bacterial capsular polysaccharides (*S. pneumoniae and H. influenzae type B*). IgG3 is particularly relevant in the primary antibody response to respiratory viral agents, as it is the most functional subclass, closely followed by IgG1, due to its superior affinity to FcεR. IgG4 is the least common subclass, accounting for only 2%–6% of the total IgG level. The relevance of IgG4 deficiency is uncertain; however, a few studies have claimed that selective IgG4 deficiency may play a pathogenic role in patients with severe infections or bronchiectasis.

In addition, there is growing evidence that PADs involve multiple non B-cell immunological defects, such as T cells, mannose-binding lectin, Toll-like receptors, antimicrobial peptides, and/or neutrophils. In line with these findings, recent studies have shown that viral infections in this population are associated with clinical deterioration. Bacterial and viral coinfections were detected in 25% of CVID patients with exacerbations of the underlying respiratory diseases.

A pathogenic mechanism of IGGSCD has been proposed: heterozygous gamma gene deletions are reported to reduce serum levels of the corresponding subclasses, and rare homozygous gene deletions have also been described.58 However, regulatory dysfunction of B lymphocytes has been suggested to be a primary mechanism in PADs.59 Immunophenotyping of the B-cell compartment has been utilized to improve the diagnosis of PADs in recent years, and patients with PADs showed reduced Ig-switched memory B cells, T helper 17 cells, and naïve T cells.

Blanco et al. revealed that patients with IGGSCD or CVID showed defects in memory B-cell subsets and plasma cells. Sohn et al. reported that the ability to proliferate and activate B lymphocytes was significantly decreased in asthmatic patients with IGGSCD compared to those without IGGSCD, and this decrease was more profound in severe asthmatic patients, indicating that functional defects in B lymphocytes exist in asthmatic patients with IGGSCD.

Immunoglobulin class isotype switching defect

These abnormalities, formerly called hyper-IgM syndromes, are rare disorders characterized by decreased serum IgG and IgA levels, associated with normal or elevated IgM levels [18]. The underlying mechanism is either an abnormality in costimulation of B and T cells at the germinal center, affecting the initiation of class isotype switching, or a dysregulation of the class isotype switching process itself. The prototype of a costimulatory defect is CD40-X-linked ligand deficiency [19-22]. CD40L deficiency not only causes a DID (dihydroimmunotropic immunodeficiency), but also a functional abnormality of T cells since this antibody deficiency is secondary to reduced CD40L expression on T lymphocytes. Consequently, CD40L deficiency is now primarily considered a T-cell abnormality [18]. Due to the T-cell abnormality, this DIH differs significantly from other DIHs in that it is characterized by the occurrence of opportunistic infections.

In addition to bacterial pneumonia, which occurs in 80% of patients, 41% present with Pneumocystis jirovecii pneumonia [22]. Severe combined immunodeficiency (SCID) is among the differential diagnoses for CD40L deficiency [23], but unlike most SCID cases, lymphocyte subpopulation analysis in patients with DIH will show a normal T-cell count. Like patients with XLA, neutropenia may be present, and CD40L patients also share an increased susceptibility to enterovirus meningoencephalitis. Furthermore, CD40L patients are prone to fatal sclerosing cholangitis secondary to Cryptosporidium parvum infection.

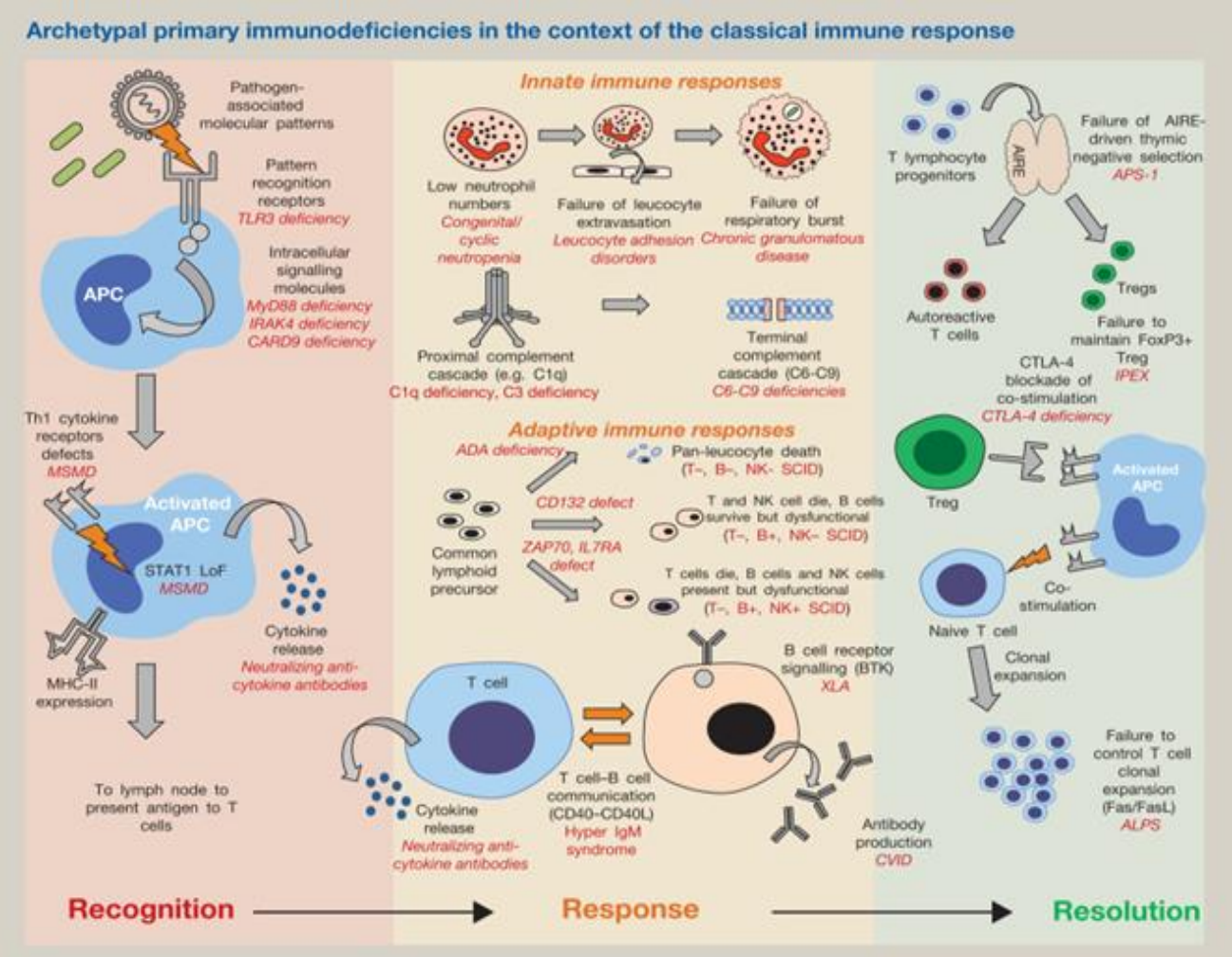


Figure 3: Immunopathology of humoral immunodeficiency

- **Clinical manifestations of primary humoral deficiencies**

Immunodeficiency should be suspected when recurrent infections are severe, complicated, resistant to treatment, or related to unusual microorganisms [9]. Infections are the most typical manifestation of immunodeficiency, but it is important to rule out other risk factors because they are also common in other conditions and in healthy individuals [9]. Upper respiratory tract infections are also less likely to be due to immunodeficiency; for example, recurrent otitis media is common in healthy children [9].

The most common presentation of immunodeficiency is recurrent sinopulmonary infections with encapsulated bacteria (S. pneumoniae, H. influenzae, etc.), which is seen particularly in antibody deficiencies (e.g., CVID, XLA, or hyper-IgM syndrome) [9]. Unexplained, severe, unusual, or persistent recurrence of infections should raise suspicion of immunodeficiency [9]. Particular attention should also be paid to the nature of the infections; for example, Neisseria meningitis (≥ 2 episodes) or any Neisseria meningitis caused by an unusual serotype (A/C/Y/W) should prompt investigation for a terminal complement pathway defect [9]. Other bacterial meningitis can be observed in asplenia, antibody defects, or early complement component defects and should prompt further investigation if associated with recurrent infections or a family history of meningitis [9].

Clinicians should also be alerted to unexplained deep infections, more than two episodes of sepsis, deep skin or organ abscesses, endocarditis, or osteomyelitis [9]. The typical example in these cases would be chronic granulomatous disease, which manifests as deep abscesses, pulmonary aspergillosis, and infections with catalase-positive bacteria [9].

Unusual infections can also point to the presence of an immunodeficiency [9]. These may include confirmed infections with environmental (non-tuberculous) mycobacteria, or episodes of atypical mycobacterial infection appearing before the age of 30, suggesting Mendelian susceptibility to mycobacteria [9]. In our case report, it was a typical mycobacteriosis caused by Mycobacterium tuberculosis. Other opportunistic infections (Pneumocystis, coccidia, cryptosporidia, Toxoplasma, CMV, etc.), infections caused by live vaccines (disseminated infection

following vaccination against varicella, yellow fever, or Bacillus Calmette-Guérin (BCG), etc.), and vaccine failures (infections or seronegativity in a previously vaccinated individual) may suggest an immunodeficiency, particularly a primary one [9].

Other persistent infectious manifestations should also concern clinicians, such as persistent unexplained chronic diarrhea with weight loss, oral thrush, or a fungal skin infection [9]. Certain complications associated with infections may also be suggestive, particularly bronchiectasis, which is very common in primary antibody deficiencies [9]. The British Thoracic Society recommends serum immunoglobulin (IgG, IgA and IgM) testing in all patients with bronchiectasis [9].

- **Management of primary antibody deficiencies**

The management of SID relies on two pillars: identifying and treating the underlying cause and preventing infections. The treatment of the etiology focuses on addressing the underlying disease process to reverse or slow down the progression of the immune deficiency whenever possible. The risk of infection varies significantly depending on the underlying condition, immunosuppressive treatment, and patient characteristics. Generally, infection risk is low in young patients without significant comorbidities receiving a single immunomodulatory agent for inflammatory diseases, while SOT and HCT recipients, patients with hematologic malignancies undergoing intensive chemotherapy, and patients with HIV infection and CD4 counts below 200 cells/mm3 are at the highest risk. Older patients with cancer and other comorbidities on combined immunosuppressive regimens are at intermediate risk.

Immunoglobulins Replacement Therapy

Immunoglobulins replacement therapy (IGRT) plays a crucial role in reducing the risk of infections in patients with hypogammaglobulinemia, particularly those with PID. While a total serum IgG level below 4 g/L is often considered a strong indicator for further evaluation, the ESID diagnostic criteria emphasize a comprehensive assessment, including Ig levels, vaccine response, and clinical history. The decision to initiate IGRT should therefore be based not solely on IgG levels, but on the overall immunological and clinical context. Studies in patients with CVID have shown that the risk of infections, particularly pneumonia, rises significantly when serum IgG levels fall below 3.0 g/L [10]. Furthermore, patients with persistent very low IgG levels (< 1.0 g/L) are generally considered at high risk for severe and potentially life-threatening infections. In such cases, IGRT is typically initiated even in the absence of a significant history of infections [10].

The consensus is that IGRT should aim to maintain trough serum IgG levels of at least 5.0 g/L [30]. Higher target levels (8–10 g/L) are advised for certain high-risk patient groups, such as those with bronchiectasis or chronic lung diseases [10]. In contrast, the role of IGRT in patients with hematologic malignancies and SOT recipients is less well established and remains controversial [10]. For selected patients with severe forms of IEI, curative approaches such as hematopoietic stem cell transplantation or gene therapy may be considered in specialized centers. While these modalities are beyond the scope of this review, they represent important therapeutic advances that complement supportive measures such as IGRT.

Antimicrobial Prophylaxis Based on Infectious Risk

Patients at high risk for infection (e.g., transplant recipients, cellular therapies recipients, HIV with CD4 counts below 200 cells/mm3) (Fig. 1) may require specific antimicrobial prophylaxis. Pneumocystis jirovecii prophylaxis is recommended in patients with cellular immunodeficiencies [14, 20]. First-line prophylaxis is trimethoprim–sulfamethoxazole (TMP-SMX), which also provides protection against Toxoplasma gondii. If TMP-SMX cannot be used, alter natives for Pneumocystis jirovecii include atovaquone or aerosolized pentamidine. Toxoplasmosis prophylaxis is also recommended in patients at high risk, including toxo plasma-seropositive HIV-infected persons with CD4 counts below 200 cell/mm3 and toxoplasma-seronegative heart transplant recipients receiving an allograft from a seropositive donor [14]. When TMP-SMX cannot be used, patients at risk for toxoplasmosis may require dapsone combined with pyrimethamine and folinic acid. Given their complexity and potential toxicities, they should preferably be pre scribed with input from an infectious diseases or immunology specialist.

Other bacterial prophylaxis may also be required in specific setting. Long-term penicillin prophylaxis is recommended in patients with active graft versus host disease (GVHD) after allogeneic HCT due to increased susceptibility to recurrent bacterial infections with encapsulated bacteria [10]. Penicillin prophylaxis is recommended for patients who have not been vaccinated against Neisseria meningitidis and are treated with the anti-C5 antibody eculizumab. The optimal duration of prophylaxis, and its necessity in vaccinated individuals, remains a matter of debate [26].

Antifungal prophylaxis with fluconazole or mold-active azoles (posaconazole) is warranted during periods of pro longed severe neutropenia in patients with hematologic malignancies receiving intensive chemotherapies and/or allogenic HCT [26]. A preemptive approach based on monitoring of galactomannan and early work-up with imaging and initiation of antifungal therapy in patients with persistent neutropenic fever can also be implemented [26]. Antiviral prophylaxis against HSV and VZV is also generally recommended in high-risk patients, particularly those with cellular immunodeficiencies [27].

CMV prophylaxis (letermovir, (val)ganciclovir) or CMV monitoring with blood PCR and preemptive therapy at detection above certain viral-load thresholds is generally reserved for transplant recipients at risk [27]. Prophylaxis for hepatitis B virus (HBV) may be needed in certain high-risk patients (e.g., patients with HBsAg + chronic infection and treated with rituximab, pro longed corticosteroid therapy, or chemotherapy) [9]. Treatment of latent tuberculosis infection (LTBI), should generally be considered, especially for patients receiving TNF-α inhibitors, prolonged corticosteroid therapy, or chemotherapy [27].

Vaccines

Vacccination is crucial for reducing infection risk, morbidity, and mortality in patients with SID. Due to the heterogeneous nature of SID and limited clinical data, vaccination recommendations are mainly based on expert opinion [28]. To maximize efficacy, vaccines must be administered as soon as immune deficiency is diagnosed or before initiating immunosuppressive therapy. Live attenuated vaccines, such as measles/mumps/rubella (MMR), live-attenuated influenza, varicella, and yellow fever vaccines should generally be avoided in immunocompromised individuals and, in some cases, by their household members, due to the risk of uncontrolled replication of the weakened pathogen in immunocompromised individuals. The immunogenicity of non-live vaccine is considered to be suboptimal in immunocompromised patients. Revaccination after receipt of HCT, SOT and cellular therapies is recommended. The quality of vaccine response in SID patients is often suboptimal, depending on the underlying disease. For this reason, household members, close contacts, and caregivers should also be vaccinated to reduce exposure risk.

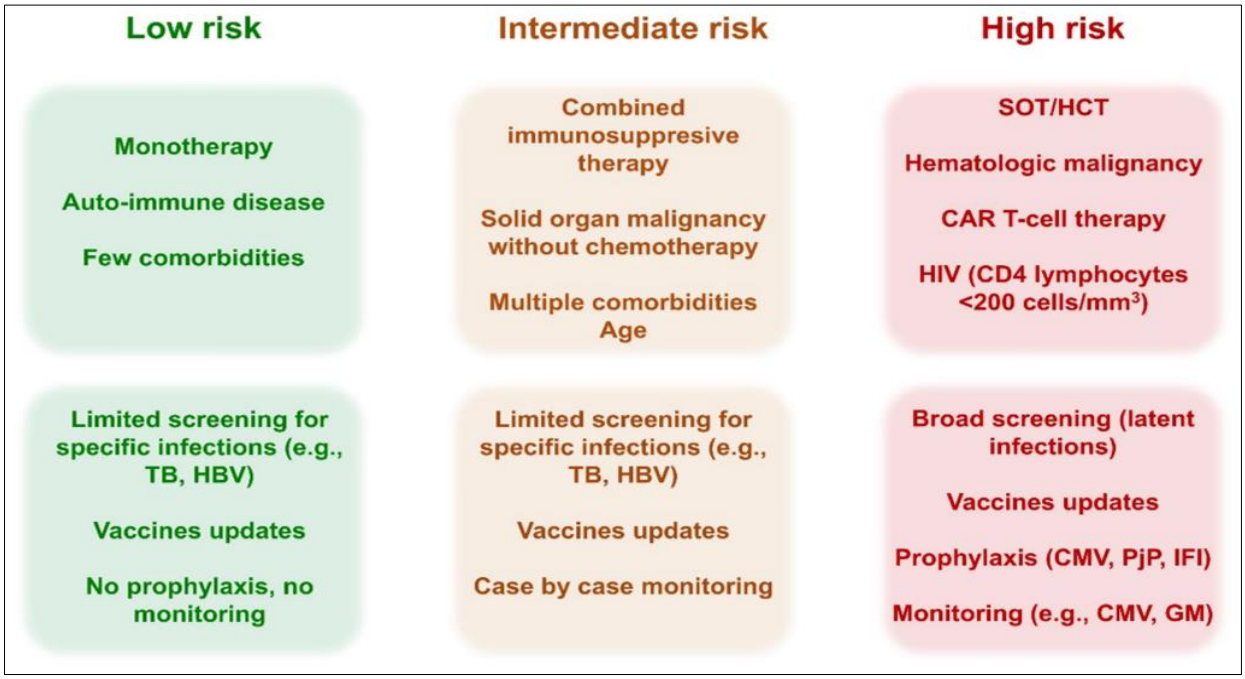


Figure 4: Conceptual framework for infectious risk stratification and preventive measures [1]

Abbreviations: TB, tuberculosis; HBV, hepatitis B virus, SOT, solid organ transplant; HCT, hematopoietic cell transplantation; CAR T-cell, chimeric antigen receptor T-cells; HIV, human immunodeficiency virus; CMV, cytomegalovirus; PjP, Pneumocystis jirovecii pneumonia; IFI, invasive fungal infection; GM, galactomannan

Special considerations regarding certain medications

Checking the medication list of any patient suspected of having an immunodeficiency is a crucial step. Some medications, such as corticosteroids, induce lymphopenia, primarily of CD4+ T lymphocytes, and can also cause hypogammaglobulinemia, although this is usually mild, rarely symptomatic, and often affects IgG [9].

Several other medications can cause secondary immunodeficiency, such as immunosuppressants like cyclophosphamide and methotrexate, newer targeted therapies, particularly anti-CD20 therapies, and other more traditional medications such as antiepileptics (carbamazepine, phenytoin, etc.) which can lead to low antibody levels, sulfasalazine, and D-penicillamine [9].

Monitoring and Prognosis of Humoral Immunodeficiency (HID)

Long-term follow-up of HID patients receiving immunoglobulin replacement therapy should focus on the early detection of chronic obstructive pulmonary disease (COPD). In addition to routine pulmonary function tests, at least one chest CT scan is recommended for these patients to rule out bronchiectasis or other pulmonary abnormalities [36]. Attention should be paid

to symptoms suggestive of non-infectious complications such as autoimmunity, granulomas, splenomegaly, and enteropathy. A decrease in memory B cells in patients with CVID is associated with a higher incidence of clinical complications [35]. Therefore, it would be beneficial to monitor this lymphocyte subpopulation in these patients, while also interpreting the results (normal values) in light of the patient's age.

CONCLUSION

Immune deficiencies are frequently encountered in the daily practice of all physicians. These practitioners must be aware of the various warning signs that may point to immunodeficiency, particularly secondary immunodeficiency, the most common condition in adults. They must also be trained to recognize the signs that may indicate primary immunodeficiency, which is not so rare, even in our adult patients. It is the responsibility of experts in the field of clinical immunology to provide ongoing training and updates to practitioners. This will allow for early intervention for patients in the future, thereby reducing the morbidity and mortality associated with immunodeficiency and improving their survival and quality of life.

Additional Information

Declaration of patient consent:

Written informed consent was obtained from the patient's family to publish this report in accordance with patient consent policies. In this report, the patient has consented to the publication of his images and other clinical information in the journal.

Competing Interests: The authors declare no conflict of interest.

Authors' Contributions:

All authors participated in the evaluation and follow-up of the patient, in the writing and correction of the case report. All the authors of the manuscript have read and agreed to its content.

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