# **Common Variable Immunodeficiency**

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Inborn errors of immunity (IEI) are multifaced diseases which can present with a variety of phenotypes, ranging from infections to autoimmunity, lymphoproliferation, and neoplasms. In recent decades, research has investigated the relationship between autoimmunity and IEI. Autoimmunity is more prevalent in primary humoral immunodeficiencies than in most other IEI and it can even be their first manifestation. Among these, the two most common primary immunodeficiencies are selective IgA deficiency and common variable immunodeficiency (CVID).

Keywords: common variable immunodeficiency (CVID) ; autoimmunity

# 1. Introduction

Autoimmunity and primary immunodeficiencies were once considered diametrically opposed; in recent decades, the attention paid to the link between the two has grown, both because they are frequently associated <sup>[1][2]</sup>, and for the possible therapeutic implications resulting from a greater insight into their pathogenesis. The dichotomy between immunodeficiencies and autoimmunity was challenged at the end of the last century by the identification of genetic diseases characterized by infections, autoimmunity, inflammation, immune dysregulation, allergies, and a predisposition to malignancies <sup>[3]</sup>.

Autoimmunity is a self-damaging immune response, caused by self-reactive specific adaptive immune responses involving antibodies, T cells, or both <sup>[<u>4</u>]</sup>; it is influenced by a number of genetic factors and caused by gene–environment interactions <sup>[<u>5</u>][<u>6</u>]</sup>. As it is usually impossible to eliminate the target antigen, chronic inflammation and consequent tissue damage occur. Previously thought to be rare, autoimmune diseases affect 3–5% of the population <sup>[<u>7</u>]</sup>, with over 100 distinct autoimmune disorders currently identified, either organ-specific or systemic <sup>[<u>8</u>][<u>9][10]</u>.</sup>

Immunodeficiencies, on the other hand, are characterized primarily by recurrent or severe infections; they are also manifestations of the dysregulation of the immune system. Researchers distinguish them into primary and secondary, the latter frequently reversible and usually caused by extrinsic factors, i.e., infections, drugs, systemic diseases <sup>[8]</sup>, which need to be ruled out if a primary immunodeficiency is suspected.

Primary immunodeficiencies (PIDs), also known as inborn errors of immunity (IEI), can be defined as a large, heterogeneous group of 485 rare diseases [11][12] caused by inherited defects of the immune system, consisting of different phenotypes, currently classified into ten categories according to the components of the immune system affected. The incidence of these forms is variable, ranging from 1:500 for the most frequent forms to 1:500,000 for the rarest ones  $[\mathfrak{Y}]$ . Taken together, the incidence of PIDs is estimated at around 1:2000 [13], but it is largely underestimated due to the heterogeneity of their clinical presentation (as said, infections, autoimmunity, autoinflammatory disorders, allergy, malignancy, and/or immune dysregulation).

A high prevalence of autoimmune diseases has been highlighted in patients with primary immunodeficiencies. Humoral deficits are the most common PIDs, accounting for around 50% of them <sup>[14]</sup>, followed by combined immunodeficiencies (T and B lymphocytes defects) accounting for 12% of them <sup>[14][15]</sup>. Selective IgA deficiency (SIgAD) is the most common PID, although it is generally asymptomatic, while common variable immunodeficiency (CVID) is the most frequently symptomatic one; around 30% of these patients have autoimmune disorders and these can even be the first clinical manifestation of CVID <sup>[16][17][18]</sup>.

## 2. Common Variable Immunodeficiency

CVID is the most common clinical primary immunodeficiency; it is characterized by hypogammaglobulinemia, with low serum IgG (2 SD below the mean for age) and low levels of IgA and/or IgM, a poor response to vaccinations, and

exclusion of secondary causes of hypogammaglobulinemia (according to the European Society for Immunodeficiencies and classified by the International Union of Immunological Society Expert Committee).

CVID is also characterized by a normal or low B lymphocytic count, normal lymphocytic phenotype, but an impaired differentiation of the germinal center B cells (in the lymph nodes) to plasma cells and memory B cells. Therefore, lymphocytes are capable of antigen recognition but not of consequent maturation to effector cells and the production of sufficient amounts of antibodies. CVID is a complex syndrome which probably comprises a variety of different diseases with different pathogenetic mechanisms, all leading to hypogammaglobulinemia of IgG and at least another antibody class, and current understanding of its pathophysiology remains still incomplete.

Its diagnosis is based on the serum levels of immunoglobulins and poor vaccine responses or vaccine failures, assessed as per the levels of specific antibodies elicited after the immunization course. For the diagnosis, a cut-off of 4 years of age has been chosen because before this age, immunoglobulin deficiency can be a transient phenomenon due to the delayed maturation of the immune system and prolongation of physiological hypogammaglobulinemia of infants <sup>[19][20]</sup>.

Treatment consists of lifelong antibodies administration, antibiotics against recurrent infections, and some cases may require tailored treatments.

### 2.1. Epidemiology

It is the second-most prevalent primary humoral deficiency after SIgAD and the most frequently symptomatic one. These two diseases share the same pathogenetic substrate, resulting in similar characteristics, and 5% of patients with SIgAD develop CVID <sup>[21][22]</sup>. Usually diagnosed in adults between the second and the fourth decade of age, it can also occur in children or in elderly people. Both sexes are equally affected, with a prevalence of 1:25,000–1:50,000 worldwide. The majority of patients have a normal life expectancy; however, it can be lowered should an autoimmune disorder or a malignancy overlap with the primary immunodeficiency.

#### 2.2. Genetics

CVID is influenced by a variety of genetic abnormalities, the majority of which are unknown and arise through de novo mutations in different genes (familiar inheritance is less frequently implicated in the disease: in 5–25% of cases <sup>[23]</sup>, CVID, SIgAD, and X-linked agammaglobulinemia can occur in the same family) <sup>[24]</sup>.

While most CVID patients may have a polygenic disease, 2–30% cases of CVID are thought to be monogenic <sup>[25]</sup>; additionally, genetic mutations are a necessary but not sufficient cause of the disease <sup>[26]</sup>. Monogenic CVIDs tend to have an autosomal dominant transmission with incomplete penetrance, or in some cases, autosomal recessive inheritance <sup>[24]</sup>. Some of these mutations also predispose to autoimmunity. The genetic heterogeneity may account for why some patients do not respond to standard supportive therapies <sup>[27][28]</sup>.

A small number of these damaging monogenic mutations have been identified, among which, polymorphisms in *TNFRSF13B/TNFRSF13C* encoding TACI and BAFF-R, respectively, and the *NFKB1* and *NFKB2*, *CD19*, *CD20*, *CD21*, and *CD81* genes are strongly associated with the disease. These monogenic defects result in abnormal B cell development at different stages, both in the lymph nodes and in the bone marrow, abnormal B cell activation, proliferation, and survival. Other genetic defects that have been identified affect T cells <sup>[29]</sup>.

CVID patients with a *TNFRSF13B/TNFRSF13C* mutation, especially if heterozygous, have a propensity to autoimmunity and lymphoid hyperplasia potentially due to a lack of the normal mechanisms of tolerance <sup>[30][31]</sup>.

Several studies have found increased concentrations of the lymphocyte-specific members of the tumor necrosis factor (TNF) superfamily in CVID, transmembrane activator and CAML interactor (TACI) receptor and its ligands, a proliferationinducing ligand (APRIL) and B cell activating factor of the TNF family (BAFF), with biological consequences that are still unclear <sup>[32]</sup>. The BAFF molecule can activate three types of the B cell transmembrane receptors BAFF-R, TACI, and B cell maturation antigen (BCMA), with higher affinity for the first one, BAFF-R, which is expressed on naïve and transitional B lymphocytes and can promote their proliferation and survival via the non-canonical NFKB signaling which ultimately increases the antiapoptotic gene *BCL-2*. The APRIL ligand has higher affinity than BAFF for the TACI receptor, which is expressed on marginal zone (MZ) and class-switched memory B cells, where defective NFKB transduction can activate the cell-cycle arrest genes with impaired maturation to plasma cells, or they can trigger apoptosis. The BCMA receptor is expressed on plasma cells; it is activated by both APRIL and BAFF but the exact cell responses induced remain unclear [33][34]. TACI and BAFF-R defects, found in 20–30% of CVID patients, impairing B cell maturation and class-switch recombination of the mature B cell, are associated with variable autoimmune manifestations <sup>[31][35][36]</sup>. However, the role of TACI and BAFF-R <sup>[37]</sup> is debated as their defects can also be found in healthy controls, therefore they may not be strictly causative for the disease <sup>[38]</sup> but may be disease-modifying.

*NFKB1* haploinsufficiency is linked to autoimmune cytopenia, enteropathy, lymphoproliferation, lymphoma. The damaging *NFKB2* variants lead to autoimmunity affecting skin, hair, and nails, and endocrinopathies, e.g., pituitary hormone deficiencies, autoimmune cytopenia [11].

Activated PI3K Delta Syndrome (APDS) has significant autoimmune manifestations <sup>[11]</sup> such as cytopenia, juvenile arthritis, glomerulonephritis, sclerosing cholangitis, and lymphoproliferation <sup>[28]</sup>.

Some monogenic defects previously associated with CVID are now considered pathogenetic for different nosological entities (according to the international classification of IEI) <sup>[11]</sup>, e.g., ICOS deficiency, characterized by low Ig, normal levels of T and B lymphocytes, autoimmune cytopenia, enteropathy, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), was previously thought to be causative for CVID but it is now associated with combined immunodeficiency (CID). Similarly, genetic mutations of *PLCy2*, previously considered pathogenetic for an autoimmune phenotype of CVID, is now regarded as an autoinflammatory disorder affecting the inflammasome: PLCy2-associated humoral deficiency and immune dysregulation (PLAID).

#### 2.3. Pathogenetic Notes on CVID and Associated Autoimmunity

The pathophysiology of CVID is rather mysterious, despite the progress in molecular biology, immunophenotyping, and genetics. The clinical heterogeneity points to the possibility of multiple different alterations of the immune system: defects of B cells, T cells, and cytokine production, resulting in deficient antigen-specific IgG synthesis in response to pathogens.

CVID is mainly a B cell dysfunction and in some patients abnormal T cells have been found. Well-established defects in B cell differentiation to plasma cells and memory B cells, with hypogammaglobulinemia and failure of specific antibody production can coexist with T cell deficits, which are expected given the dependence of B lymphocyte function on T cells. Overall B cell count is normal in 90% of patients with CVID; they have a low number of isotype-switched plasma cells and memory B cells, which produce antigen-specific IgG and IgM/IgA required for secondary humoral responses (the deficiency in the antigen selected repertoire suggests a defect in the germinal centers, where T-dependent antibody responses take place) <sup>[39][40]</sup>.

The peripheral selection of memory B cells appears to be impaired in CVID with an autoimmune phenotype: a low number of switched memory B cells and CD27+, based on total blood lymphocytes, is an independent risk factor for autoimmune disease, granuloma formation, and splenomegaly <sup>[41][42]</sup>.

In addition to the above, a few patients have an increased percentage of circulating transitional B cells often associated with low total B cell counts and autoimmunity  $\frac{[29][43]}{2}$ . Moreover, new studies are investigating a possible role of the  $\kappa$ : $\lambda$  ratio evaluation in transitional B cells in order to separate the subgroup of CVID with an autoimmune phenotype from the other subsets of patients with CVID  $\frac{[44]}{2}$ .

An unusual population of polyclonal B cells characterized by a low expression of CD21 has been observed in CVID and in various autoimmune diseases, such as SLE and RA. These cells resemble naïve B cells that are IgM + IgD + but with a higher expression of costimulatory molecules allowing for a potential function as antigen presenting cells <sup>[45]</sup>, and they display a high prevalence of autoreactive BCR <sup>[46]</sup>. The expansion of activated CD21low B cells has been observed in a number of patients, predominantly those with autoimmunity, lymphoproliferation, splenomegaly, and evidence of chronic immune activation  $^{[47][48]}$ .

CVID patients have been grouped based on the underlying B cell defects by flow cytometry, according to the EUROclass, Freiburg, Paris, and EuroFlow classifications <sup>[49]</sup>, and this work constitutes the largest basis for the clinical– immunophenotypic correlations mentioned, among which include autoimmunity. In particular, the EUROclass system distinguishes patients based on the total B cell count, switched memory B cells, transitional B cells, and CD21 expression. The Freiburg classification analyzes memory class-switched B cells and CD21 expression. The Paris classification is based on memory class-switched B cells and total CD27+ B lymphocytes. The EuroFlow consortium developed a PID orientation and screening tube aiming to standardize the lymphoid PID identification <sup>[50]</sup>, separating these patients from those affected by non-lymphoid PIDs and further grouping them into severe combined immunodeficiency (SCID), combined immunodeficiency (CID), immune dysregulation disorder (ID), and CVID; the most discriminative populations were the memory B and switched memory B cells, total T cells, CD4+, and naïve CD4+ cells.

A minority of patients have BCR abnormalities, found in the bone marrow B cell precursors at the pro-B stage. These patients display a decreased diversity of naïve BCR, e.g., decreased rearrangement, decreased V gene replacements (which normally counteracts autoimmunity), and abnormal expansion of unmutated B cell clones <sup>[51][52]</sup>. Although impaired B cell germinal center activation is commonly viewed as causative in CVID, these data may give additional explanations for the increased prevalence of autoimmunity, immunodeficiency, and lymphoma in CVID <sup>[53][54]</sup>.

A few studies investigated the role of innate immune dysregulation in the pathogenesis of CVID, among which defective TLR9 activation was associated with the expansion of autoreactive B cells in immune cytopenia <sup>[55]</sup>, and it is hypothesized that DNA mismatch repair can lead to autoimmune and cancer susceptibility in CVID <sup>[53][54]</sup>.

A subgroup of CVID patients have T cell abnormalities. The coexistence of T and B cell alterations can explain both the hypogammaglobulinemia and the other complications: autoimmunity, lymphoma, inflammation. In fact, these patients have a more severe phenotype, presenting with gastrointestinal disease, splenomegaly, granuloma, and lymphoma [56][57].

T cell abnormalities in patients with autoimmunity and CVID may include alterations in the number of Th1 CD4 or CD8, which have been found to be decreased in some studies and increased in other studies <sup>[58]</sup>. In the first case, this may result in both susceptibility to intracellular pathogens (viruses and bacteria) and autoimmunity (especially cytopenia) <sup>[59]</sup>. On the other hand, in contrast to the previous theories of T cell exhaustion, other studies suggest that chronically activated T CD4+ and or CD8+ are common in patients with autoimmunity <sup>[60]</sup>, lymphoid proliferation, and splenomegaly <sup>[61]</sup>. These conflicting data may account for the different pathogenetic mechanisms of the different forms of CVID.

Human follicular helper T (TFH), a subset of CD4+ lymphocytes, contribute to B cell activation and differentiation and the generation of long-lived antibody responses—their defects cause humoral immunodeficiency, autoimmunity, and T cell lymphoma <sup>[62]</sup>.

Abnormalities of Tregs/Th17 have been reported in CVID as well as in SIgAD. Both T Regs and Th17 are produced under similar inflammatory environments; however, the former turns down inflammation and the latter promotes it.

It is debated whether the Th17 profile in CVID patients is positively associated with autoimmune diseases such as immune thrombocytopenia, autoimmune hemolytic anemia, rheumatoid arthritis, psoriasis, and lupus <sup>[63][64][65]</sup>. Defects of Th17 result in a loss of antimicrobial immunity at mucocutaneous sites—promoting a proinflammatory environment where autoimmunity is more likely to develop <sup>[66]</sup>. In particular, Th17 cells produce the IL-17 family of cytokines, among which IL-17A is involved in the defense against extracellular pathogens, and autoimmune and allergic diseases <sup>[67]</sup>. Furthermore, a decline in the Th17 count has been linked to an increase in CD21low B cells <sup>[66]</sup>, which are associated with an autoimmune phenotype.

The role of T regulatory cells is well established in the peripheral tolerance as well as in autoimmune diseases <sup>[68]</sup>. Defects of Tregs CD4+CD25+ have been documented in CVID <sup>[69][70]</sup>. These cells produce IL10 which suppresses potentially dangerous excessive peripheral immune responses, reducing tissue damage, and helps maintain peripheral tolerance (FOXP3 is the major transcription factor converting naïve T cells to Tregs and serving as a lineage specification factor). Defects in this gene cause a paucity of Tregs, with autoimmune and allergic disorders, cancers, autoimmune polyendocrinopaties, and IPEX syndrome (Immunodysregulation, Polyendocrinopathy, and Enteropathy, X-linked) classically presenting with the triad: intractable diarrhea, type 1 diabetes, and eczema in male children <sup>[71]</sup>.

CVID patients exhibit a clonal and constricted TCR repertoire <sup>[72]</sup>. Defects in TCR signaling in CVID have been described: defects in the CD40 L costimulatory receptor in CD4+ and CD8+ results in the defective amplification of TCR signal transduction <sup>[56][73]</sup>. Defects in TNF receptor II causing reduced TARF1 expression and reduced T cell proliferation have been documented <sup>[69][74]</sup>.

Finally, in the last decade, the possible link between gut microbiota and systemic inflammation, autoimmunity, and immune-mediated disorders has been investigated, but only a few studies have focused on the microbiota in CVID. A reduced microbial diversity was found in CVID <sup>[75]</sup>. Also, CVID with inflammatory/autoimmune complications seem to have a further reduced microbial diversity than the "infection only" phenotype of CVID <sup>[76]</sup>. Bacterial overgrowth and pathological bacterial translocation has been observed: microbial products can pass from the inflamed gut mucosa via the leak pathway across the tight junctions into the bloodstream, contributing to low-grade systemic inflammation and lung and liver damage in CVID <sup>[77]</sup>. The translocation of foreign antigens may give rise to either tolerance or tissue damage

through the mechanisms of molecular mimicry (similarities between self and non-self antigens) and the subsequent activation of autoreactive T/B cells <sup>[78]</sup>.

Lastly, bidirectional interactions between the intestinal bacteria and gut mucosa have been studied, and they may be the pathogenetic loop between microbiota and systemic inflammation <sup>[79][80][81]</sup> (e.g., bacteria can induce enterocyte inflammasomes and the production of NLRP3 and NLRP6 through IL-18 and CCL5 production, which can cause increased vasopermeability and the passage of microbial components into the bloodstream).

#### 2.4. Clinical Manifestations

Not only genetic heterogeneity is observed but also phenotypic heterogeneity. Five clinical phenotypes of CVID have been identified (see **Table 1**) according to Chapel et al. [82] each one with a different prognosis, and over 80% of patients display just one of them.

Clinical Phenotypes	Clinical Features
No complications: infections only	Recurrent/persistent respiratory/gastrointestinal infections
Autoimmune disease	Cytopenia, rheumatologic disease, endocrinopathy, dermatologic manifestations
Predominant enteropathy	Non-infectious diarrhea, celiac-like, IBD-like, atrophic gastritis, liver disease
Lymphocytic organ infiltration	Lymphocytic enteropathy, granulomas, splenomegaly, unexplained hepatomegaly, persistent lymphadenopathy, and/or lymphoid interstitial pneumonia
Lymphoid carcinoma	Non-Hodgkin lymphoma

**Table 1.** CVID clinical phenotypes and their main characteristics.

Still, there is no universal consensus and some of these clinical phenotypes may partially overlap (see below). Patients with non-infectious manifestations have a higher mortality risk than those infections only.

The most common manifestations of CVID are recurrent **infections** because of the low levels of antibodies: sinuspulmonary infections caused by capsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*), atypical germs (Mycoplasma), viruses (Herpes), and gastrointestinal pathogens (Giardia lamblia, Salmonella, Campylobacter, etc.), similar to those encountered in SIgAD. Patients who experience mild infections and no other complications are also defined as "infections only" <sup>[82]</sup>, and have a more benign clinical course as well as a longer survival rate compared to those with different phenotypes. These persistent/recurrent infections can promote permanent organ damage of the lungs and gut, respectively, as well as bronchiectasis and interstitial lung disease, chronic colitis, and malabsorption syndromes with celiac-like/IBD-like features, in addition to acting as a trigger for the development of lymphoproliferation, autoimmunity, and cancer. Before the second decade of the last century, until the advent of immunoglobulin replacement therapy, infections were the most common cause of mortality for CVID patients.

Currently, therapy for CVID is still centered on lifelong immunoglobulin administration and antibiotic use, aiming to stop the cycle of persistent infections, as well as infection prevention through vaccination with inactive agents <sup>[B3]</sup>. This therapy has no direct effect on most autoimmune or severe lymphoproliferative manifestations of CVID, for which immunosuppressants or allogenic hematopoietic stem transplantation <sup>[B4]</sup> may be required, respectively. However, IgG replacement proved beneficial in comorbid autoimmune cytopenia: ITP and AIHA <sup>[B5]</sup>. Immunoglobulin infusions, either intravenous or subcutaneous, prove to be equally effective and safe; while intravenous administration is performed in the hospital setting, subcutaneous infusions allow the patient to self-treat or be treated at home, maintaining a more stable Ig level <sup>[B6]</sup>. Although here is little evidence to develop universal guidelines, the usual dose of Ig that is prescribed ranges between 400 to 600 mg/kg body weight per month. The subcutaneous dose is divided into once or twice a week or once every two weeks; the intravenous dose is usually administered once a month or every 3 weeks because the half-life of intravenous Ig is close to 30 days. Also, host factors influence the immunoglobulin half-life: concomitant respiratory or gastrointestinal chronic disease, protein-losing conditions, renal or hepatic dysfunction, pregnant patients or patients with Fc receptor variants may have a reduced Ig half-life. Physicians monitor serum IgG levels at 6–12 month intervals to adjust the therapy [<sup>B27][B8]</sup>.

Approximately 25% of CVID patients develop **autoimmune diseases**, e.g., autoimmune thrombocytopenia, autoimmune hemolytic anemia, pernicious anemia, Addison disease, thyroiditis (Hashimoto/Graves), rheumatoid arthritis. Also, 10% of patients with CVID may experience malignancies, i.e., non-Hodgkin lymphoma or more rarely, gastric carcinoma. Of note,

not all primary B cell deficiencies are associated with autoimmune or inflammatory disorders and malignancies, in fact these conditions are rarely observed in X-linked agammaglobulinemia, which affects early B cell development, but they are prevalent in CVID <sup>[89][90]</sup>. This suggests that CVID represents a more global form of immune dysfunction.

**Predominant enteropathies** affect around 10–30% of CVID patients <sup>[82][91]</sup>; there is no universal consensus for their definition, as they can be based on symptoms or on histopathological findings <sup>[92]</sup>. Enteropathies are influenced by infections, autoimmunity, and immune dysregulation with lymphoid infiltration. As in the case of autoimmunity, polyclonal lymphoid infiltration, and malignancy, enteropathies are usually "late complications" occurring in adulthood, but may also be found in children <sup>[93]</sup>. They can affect different organs: the intestine, the gastro-duodenal tract, or the liver.

Enteropathies can range from the usual presentation with recurrent diarrhea (9–60% cases) <sup>[91]</sup> to celiac-like features not responsive to a gluten-free diet or are IBD-like. The most severe cases of malabsorption result in significant weight loss, protein loss, among which also immunoglobulins are lost; these patients may have increased intraepithelial lymphocytic infiltration, histological features similar to GVHD, and require parenteral feeding <sup>[94]</sup>.

The duodenal celiac-like pattern, with negative celiac antibody tests, not responsive to gluten-free diet, characterized by villous atrophy and intraepithelial lymphocytosis, is common in patients with CVID-associated enteropathy and may be due to the composition of the gut microbiota, immune dysregulation, but not gluten sensitivity <sup>[95][96]</sup>.

Atrophic gastritis has been reported in less than 20% of CVID patients. Although previously thought to be associated with *H. pylori* infection, atrophic gastritis seems to be a consequence of the immune dysregulation of which H pylori infection may be only a trigger [97][98].

Liver disease is seen in approximately 10% of CVID patients, more commonly with alterations of lab values (commonly, elevated alkaline phosphatase), biliary obstruction (primary sclerosing cholangitis, primary biliary cholangitis) <sup>[82]</sup>, and nodular regenerative hyperplasia (NRH): a cause of cirrhosis or noncirrhotic portal hypertension with hypersplenism, thrombocytopenia, and neutropenia. Some patients develop autoimmune hepatitis (AIH) in the context of nodular regenerative hyperplasia, suggesting a possible autoimmune substrate for NRH <sup>[99]</sup>.

**Polyclonal lymphoid infiltration** is an expression of the immune dysregulation in CVID, presenting in various forms: persistent lymphadenopathies, non-infectious enteropathy, and splenomegaly are rather frequent; less commonly, liver infiltration with hepatomegaly, liver nodules, and lymphoid interstitial pneumonia <sup>[100]</sup>. As with the other non-infectious complications, lymphocytic infiltration is unaffected by immunoglobulin replacement therapy.

Splenomegaly can occur in adults and children; patients with hypersplenism and autoimmune thrombocythemia or autoimmune hemolytic anemia which previously required splenectomy can be treated with immunosuppressive drugs or antimetabolites [100][101].

Chronic multisystemic granulomatous manifestations can be a challenging "sarcoidosis mimic" <sup>[102]</sup> not to be confused with chronic granulomatous disease (CGD), the genetic phagocyte defect. Affecting 10–20% patients with CVID, granuloma formation targets different organs including the liver, spleen, gut, and lungs. For reasons that are still unclear, granulomatous disease is associated with immune thrombocytopenic purpura (ITP) or autoimmune hemolytic anemia (AIHA) <sup>[103]</sup>.

Like autoimmune diseases, granulomatous disease can also be the first manifestation of CVID, years prior to the development of hypogammaglobulinemia. Histologically, the non-caseous granulomas found resemble sarcoidotic ones.

In some patients, granulomas can cause an inflammatory bowel disease similar to Crohn's disease. Lymphoid infiltrates in the lung tissue cause granulomatous lymphocytic interstitial lung disease (GLILD) but there need not necessarily be granuloma according to the current definition <sup>[104]</sup>. GLILD is the most common and the most severe interstitial lung disease (ILD) in CVID, in some instances causing a rapid decline in respiratory function, heart-lung failure, and reduced survival. CVID patients develop not only restrictive lung diseases but also obstructive ones like asthma.

**Lymphoid malignancies** have been reported in up to 7–8% CVID patients <sup>[105]</sup>, especially extranodal non-Hodgkin B cell lymphoma (NHL) and extranodular marginal B cell lymphoma, previously known as mucosal associated lymphoid tissue lymphomas (MALT) <sup>[106]</sup>, therefore it is important for the clinician to raise awareness among CVID patients of their risk. Mostly occurring in adulthood (fourth–fifth decade), in some rare cases, NHL can be the first manifestation of CVID in the pediatric population <sup>[107]</sup>. Various mechanisms of increased susceptibility to lymphoid neoplasms have been postulated in CVID: B and T cell abnormalities, DNA mismatch repair, recurrent infectious triggers, such as Epstein–Barr virus (EBV)

<sup>[108]</sup>, the inflammatory substrate generated in infectious or autoimmune conditions, and lastly, immunosuppressive treatment. In particular, EBV infection can cause the polyclonal activation, replication, and immortalization of B cells. *H. pylori* has been associated with gastric lymphomas (which can be reversed with antibiotic therapy). In general, recurrent infections lead to repetitive stimulation and hyperplasia of mucous associated lymphoid tissue, giving rise to lymphoid nodular hyperplasia (NLH) which is a risk factor for lymphoma. Also, the combination of chronic inflammatory disorders (such as IBD-like or celiac-like diseases) and their immunosuppressive treatment increases the risk for malignancies. Among the different types of lymphomas which can arise in these patients, MALT lymphomas deserve particular attention, as they can develop in the gastrointestinal tract, in the bronchial-associated mucosa, or in the salivary glands, where they are challenging to detect, both because their symptoms are masked by local inflammation and because histologically they can be difficult to differentiate from reactive infiltrates <sup>[55]</sup>.

The substrate of chronic inflammation and lymphoproliferation also predisposes 10% of patients with CVID to develop neoplasms, gastric adenocarcinoma, and B cell lymphoma, respectively. In one study, gastric carcinoma was the second-most common neoplasm and the leading cause of death in CVID patients <sup>[109]</sup>.

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