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Common Variable Immunodeficiency-associated Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD): state of the art

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Common Variable Immunodeficiency-associated Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD): state of the art

Doença Granulomatosa e Linfocítica Intersticial Pulmonar (GLILD) relacionada com a Imunodeficiência Comum Variável: estado da arte

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Resumo

A imunodeficiência comum variável (IDCV) é uma das imunodeficiências primárias mais comummente diagnosticadas em adultos, caraterizando-se por uma diminuição da IgG e da IgA e/ou IgM, além de uma incapacidade na produção de anticorpos específicos em resposta a infeção ou imunização específica. Os doentes com IDCV são, portanto, mais suscetíveis a infeções oportunistas, particularmente infeções bacterianas do trato respiratório e gastrointestinal. Verifica-se que até um terço dos doentes com IDCV podem desenvolver uma forma de envolvimento pulmonar intersticial entitulada de “doença granulomatosa e linfocítica intersticial pulmonar” (GLILD), sendo essa a doença parenquimatosa difusa mais comummente encontrada na IDCV e que se associa a um aumento do risco de mortalidade.

O enfoque do projeto consiste na apresentação do estado da arte sobre a GLILD relacionada com a IDCV, através da realização de uma revisão narrativa da literatura científica. Esta doença, de etiopatogenia ainda não totalmente elucidada, corresponde a uma complicação rara, não infeciosa, traduzida por envolvimento difuso do parênquima pulmonar com coexistência histológica frequente de granulomas não necrotizantes, pneumonia intersticial linfóide e bronquite folicular e/ou hiperplasia linfóide. Extravasando o envolvimento intersticial pulmonar, em determinados doentes a GLILD pode acompanhar-se de linfadenopatias, esplenomegalia e possível envolvimento granulomatoso extrapulmonar.

A existência de uma elevada suspeição para a doença é fulcral para o seu reconhecimento. Em doentes com IDCV, o aparecimento recente de determinadas manifestações clinico-radiológicas associadas a algumas alterações laboratoriais podem remeter para a hipótese de GLILD. Contudo, a confirmação histológica por biópsia pulmonar é considerada indispensável para um diagnóstico confiante. Por compreender um componente de inflamação granulomatosa com possibilidade de manifestações multissistémicas e dado o risco aumentado de neoplasias hematológicas em doentes com IDCV, é importante diferenciar a GLILD primeiramente das hipóteses de sarcoidose e linfoma pulmonar. Apesar da ausência de consenso relativamente à abordagem terapêutica mais adequada, os regimes de tratamento passam frequentemente por corticoterapia sistémica, exclusiva ou associada a agentes imunossupressores, sendo a azatioprina e o rituximab considerados os mais promissores. Previamente ao início deste tipo de terapêutica deve ser assegurada a normalização do nível de IgG sérica.

Mais recentemente, a GLILD tem sido progressivamente reconhecida como doença intersticial pulmonar no contexto de outras imunodeficiências primárias para além da CVID, o que vem atestar a necessidade de uma adequada sensibilidade clínica para esta entidade nosológica durante a avaliação especializada de doentes com patologia deste espectro. A validação de biomarcadores de doença e a necessidade de melhorar o nível de evidência da abordagem terapêutica constituem hoje prioridades na investigação científica da GLILD.

Palavras chaves

Imunodeficiência Comum Variável; Hipogamaglobulinémia; Imunodeficiências primárias; Doença Granulomatosa e Linfocítica Intersticial Pulmonar; Doença Intersticial Pulmonar; Patogénese; Radiologia; Histopatologia; Tratamento; Sarcoidose.

Abstract

Common variable immunodeficiency (CVID) is one of the commonest primary immunodeficiencies diagnosed in adults and is characterized by a decreased IgG e IgA and/or IgM, in addition to an impaired production of specific antibodies in response to infections or specific immunizations. CVID patients are, therefore, more susceptible to opportunistic infections particularly bacterial infections of the respiratory and gastrointestinal tracts. Up to one third of patients with CVID may develop a form of interstitial lung involvement recognized as “Granulomatous and Lymphocytic Interstitial Lung Disease” (GLILD). This is the most common diffuse parenchymal lung disease found in CVID and is clearly associated with an increased risk of mortality. This narrative review aims to present the state of art of GLILD by summarizing the best scientific evidence available in the medical literature.

This disease, whose etiopathogenesis has not yet been fully elucidated with unknown pathogenesis, corresponds to a rare, non-infectious complication, translated into a diffuse parenchymal lung disease frequently with histological coexistence of non-necrotizing granulomas, lymphocytic interstitial pneumonia and follicular bronchiolitis and/or lymphoid hyperplasia. Beyond the interstitial lung involvement, in some patients GLILD can be found associated to lymphadenopathies, splenomegaly and extrapulmonary granulomas.

A high level of suspicion is crucial to recognize the disease. The recent appearance of certain clinical and radiological manifestations associated with some laboratory features can suggest for the disease. However, histological confirmation by lung biopsy is considered essential for a confident diagnosis. Comprising a granulomatous inflammation with a potential for multisystemic manifestations and given the increased risk for hematological malignancy in CVID, the differentiation of GLILD primarily from sarcoidosis and pulmonary lymphoma is of the upmost importance.

Despite the lack of consensus on the most appropriate therapeutic approach, treatment regimens often include systemic corticotherapy, exclusive or associated with immunosuppressors, with azathioprine and rituximab being considered the most promising. Normalization of serum IgG levels should be achieved prior to the start of this therapeutic regimen.

More recently, the occurrence GLILD has also been progressively recognized in other primary immunodeficiencies beside CVID, attesting to the importance of an adequate awareness towards this entity. Validating disease biomarkers and improving the evidence underlying these treatment approaches are considered today as key research priorities.

Keywords

Common Variable Immunodeficiency; Hypogammaglobulinemia; Primary immunodeficiencies; Granulomatous and Lymphocytic Interstitial Lung Disease [GLILD]; Interstitial Lung Disease; Pathogenesis; Radiology; Histopathology; Treatment; Sarcoidosis.

List of Abbreviations and Acronyms

AIHA - Autoimmune hemolytic anemia

BAFF - B cell-activating factor

BAL - Bronchoalveolar lavage

BALT - Bronchus-associated lymphoid tissue

OP - Organizing pneumonia

CTLA-4 - Cytotoxic T lymphocyte associated protein 4

CT – Computed tomography

CVID - Common variable immunodeficiency

DLCO – Diffusion capacity of the lungs for carbon monoxide

DWI - Diffusion weighted imaging sequences

EBV - Epstein-Barr virus

FDG PET-CT - 2-[(18)F]-fluoro-2-deoxy-d-glucose positron emission tomography and computed tomography

GLILD - Granulomatous and lymphocytic interstitial lung disease

HHV8 - Human-herpes virus type 8

HRCT – High-resolution computed tomography

Ig - Immunoglobulin

ILD - Interstitial lung disease

INF- γ – Interferon-gamma

ITP - Immune thrombocytopenic purpura

IVIg - Intravenous immunoglobulin

KCO – Carbon monoxide transfer coefficient

LIP - Lymphocytic interstitial pneumonia

LRBA - Lipopolysaccharide-responsive beige-like anchor

MALT lymphomas - Mucosa-associated lymphoid tissue lymphomas

MAPK - Mitogen-activated protein-kinase

MRI – Magnetic resonance imaging

NFκB - Nuclear factor kappa B

NHL - Non-Hodgkin lymphoma

PBL – Peripheral blood lymphocytes

PFT - Pulmonary function tests

PCR - Polymerase chain reaction

RAG - Recombination-activating gene

SCID - Severe combined immunodeficiency

TACI - Transmembrane activator and calcium-modulating cyclophilin ligand interactor

TNF – Tumor necrosis factor

XIAP - X-linked inhibitor apoptosis protein

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I. Introduction

Common variable immunodeficiency (CVID) is one of the most frequent primary immunodeficiencies. It consists of an heterogenous syndrome characterized mainly by hypogammaglobulinemia and recurrent infections and is also associated with a higher risk of autoimmune or neoplastic conditions. Respiratory tract infections in CVID frequently consists of a variable association of chronic sinusitis, chronic otitis media, bronchitis and pneumonia [1, 2]. Within the non-infectious manifestations, CVID patients may present interstitial lung disease. (ILD) [3] In fact, the presence of secondary organizing pneumonia, hypersensitivity pneumonitis, nonspecific interstitial pneumonia have been reported in CVID patients. Approximately two third of CVID patients with ILD present a diffuse non-infectious pneumonitis known as “granulomatous and lymphocytic interstitial lung disease” or “GLILD”. [4, 5] Despite various reports on this form of interstitial lung disease in CVID patients, little is known about its pathology, evolution and appropriate management. [6, 7]

The accurate prevalence of CVID is unknown but is estimated to lay between 1:100,000 and 1:10,000 of the population. [3] After specific isolated antibody deficiencies CVID is the most commonly primary immunodeficiency diagnosed in adulthood. [3] Age of symptom onset generally follows a bimodal curve, commonly in the first and third decades of life, without clear gender differences. [3] The mean age at diagnosis is 42 ± 16 years old (range of 11-71 years). [8] Remarkably, a retrospective European cohort study showed a 4-5 years delay between symptom onset and the final diagnosis of CVID. [2] Other studies found an average delay of six to eight years until diagnosis. [3]

The diagnosis assumption of a probable CVID case is based on clinical criteria such as recurrent infections; autoimmune disorders; granulomatous disease; lymphoproliferation and/or a family history of antibody deficiency.[9] The reduced antibody production of IgG and of IgA, with or without low IgM levels, has to be measured in two different times and the measurement lower than 2 standard deviations of the normal levels for their age.[9] In addition, finding an absence of protective antibody levels despite vaccination and/or a decreased switched memory B cells lower than 70% of age-related normal value also supports a probable diagnosis. [9] Furthermore, establishing a sound diagnosis of CVID makes it necessary to exclude secondary causes of hypogammaglobulinemia and for the patient to be at least 4 years old (despite a possible earlier onset of symptoms). [9]

Immunodeficiencies in subjects younger than 4 years old or with, otherwise, incomplete criteria may be classified as “unclassified-antibody deficiency”. [3] No evidence of profound T cell deficiency, defined by CD4 numbers/µL: 2-6y (years old) <300, 6-12y <250; >12y <200 and the percentage of naïve of CD4 : 2-6y <25%, 6-16y <20%, >16y <10%. (Table 1). [9]

Table 1. Clinical criteria for probable diagnosis of CVID

At least one of:	• Increased susceptibility to infection • Autoimmune manifestations • Granulomatous disease • Unexplained polyclonal lymphoproliferation • Affected family member with antibody deficiency
AND	• Marked decrease of IgG and marked decrease of IgA, with or without low IgM levels (measured at least twice; < 2 SD of age-related normal value)
AND at least one of the following	• Poor antibody response to vaccines (and/or absent iso-hematogglutinins) i.e., absence of protective levels despite vaccination • Low switched memory B cells (<70% of age-related normal value)
AND	• Secondary causes of hypogammaglobulinemia have been excluded (e.g., infection, protein loss, medication, malignancy)
AND	• Diagnosis established after the 4th year of life (symptoms may be present before)
AND	• No evidence of profound T-cell deficiency, defined as 2 out of the following (y=years of life) - CD4 numbers/ µL: 2-6y <300, 6-12y <250, >12y <200 - % naive of CD4 : 2-6y <25%, 6-16y <20%, >16y <10%, T cell proliferation absent

Adapted from European Society for Immunodeficiencies (ESID) Registry – Working Definitions for Clinical Diagnosis of PID (Primary Immunodeficiency). (Latest version: November 2019) [9]

The immune defect at issue results from a B-cell dysfunction, an impairment of T-cell function and an insufficient help for antibody production. More specifically, the majority of patients show a reduced number and percentage of switched memory B cell (for 80% of patients, circulating B lymphocytes cells represent more than 1% of lymphocytes) suggesting a disturbed germinal center function which is decisive for T-dependent antibody response. [3, 10] A relative T-cell dysfunction has been found in up to 50% of patients and probably contributes to the heterogenous clinical manifestations in CVID. [10, 11] T cells can comprehend a decrease in circulating CD4 T cells, specifically naïve CD4 T cells, antigen specific T cells and impaired proliferation, activation and secretion of some cytokines. [3] Recently, other defects have been demonstrated related to thymic maturation, monocyte/dendritic cells and impaired innate immune responses.[3]

Several classifications have been proposed for CVID patients. The first classification, developed by Bryant et al., classify CVID patients based on the B cell production of IgG and IgM after exposure to anti-IgM and IL-2 (Interleukin 2*)*. [12]

Warnatz et al. proposed the “Freiburg scheme” in an attempt to show an intercorrelation of lymphocytes subtypes and clinical manifestations. Patients are classified according to the quantification of switched memory B cell ($CD27^+$, IgM^-, IgD^-) amongst peripheral blood lymphocytes (PBL). Patients presenting switched memory B cell ($CD27^+$, IgM^-, IgD^-) <0,4 % of PBL are consequently divided according to the expression of $CD21^-$. Thus, the subgroup of patients presenting an increased expression of $CD21^-$ are more likely to present splenomegaly and autoimmune disease. [10] Notably, patients presenting low levels of B cell numbers or granulomas were excluded in the study. [13]

Piqueras et al. proposed the “Paris scheme” based on the quantification of the expression of CD27 and IgD markers among B cells. The CD27 surface marker, from the receptor of TNF gene family, is largely expressed by T cells and by a subpopulation of B cell. [14] Therefore patients were divided according to the quantification of switched memory B cell (IgD^-, $CD27^+$) and non-switched memory B cell (IgD^+, $CD27^+$). Patients with a reduced switched memory B cell and non-switched memory B cell are more prone to present granulomatous disease, lymphoid proliferation and splenomegaly. In addition, subgroup of patients with reduced switched memory B cell but normal non-switched memory B cell frequently present splenomegaly. However, autoimmune manifestations are equally reported among groups of patients. [10, 14]

The EUROclass have suggested a convergence of the two previous classifications above mentioned for CVID patients. The percentage of circulating B cells is first measured with the majority of patients (90%) usually presenting more than 1% of B cells among total lymphocytes. This group is consequently divided according to the percentage of switched memory phenotype ($CD19^{+}$, $CD27^{+}$, IgM^{-}, IgD^{-}), the percentage of transitional B cells ($CD19^{+}$, $CD38^{++}$, IgM^{+}) and the expression of low levels of CD21($CD21^{low}$ B cells) on peripheral blood. [10] The incidence of splenomegaly is significantly associated with higher expansion of $CD21^{low}$ B cells, while a severe reduction of switched-memory B cell is associated with a higher incidence of granulomatous disease and an increase of transitional B cells with lymphadenopathy. [10]

The cause of these immune impairments remains undetermined in 98% of cases. [3] Although most cases are sporadic, several mutations have been associated with autosomal recessive and dominant inheritance. [15] This small proportion of cases present deficiencies in inducible co-stimulator (ICOS), CD19, CD20, CD21, CD81, lipopolysaccharide-responsive beige-like anchor (LRBA), B cell-activating factor (BAFF) receptor and CXCR4. [15] Defects on genes for NF-κB 2 and PIK3CD have been associated with a pattern resembling dominant inheritance. The latest, causing a CVID-like phenotype, is characterized by an early onset, autoimmune features and adrenal insufficiency. [15]

CVID patients can be divided according to clinical manifestations in three phenotypes. An "infection only phenotype"[3] commonly defines a subgroup of patients suffering only from infections (bacterial, viral or opportunistic) and their related-complications (bronchiectasis, cavities and post-infection scarring) [16] and generally presents a near-normal life expectancy if timely treated with Ig (Immunoglobulin) replacement and antibiotics when necessary. [15] There is a second phenotype defining patients who, beside recurrent infections, may go on to develop non-infectious complications, encompassing diffuse lung disease, granulomatous disease, liver abnormalities, gastro-intestinal disease, lymphoid hyperplasia, and/or solid or hematological malignancies [3, 15]. This subgroup of patients frequently show reduced life expectancy and quality of life. [15] Finally, a third group, described as "CVID-like", is caused by defects in T cell maturation and is characterized by early-onset bronchiectasis, autoimmune disease and persistent viral infections. Some mutations (LRBA deficiency and gain function mutations in the P110δ and the p85α subunits of PI3 kinase) have been associated to "CVID-like" phenotype however its clear affiliation to "CVID" or to a different type of hypogammaglobulinemia remains uncertain. [15]

II. Objectives and methods

This narrative review aims to present the state of art of GLILD by summarizing the best scientific evidence available in the medical literature. Relevant papers were selected in the english language, up to january 2020 using the keywords “common variable immunodeficiency”, “hypogammaglobulinemia”, “granulomatous and lymphocytic interstitial lung disease” and “sarcoidosis”. The research was initially pursued in DynaMed, PubMed and Web of Science databases. Then the reference lists of included studies were also checked for additional references. Relevant articles were selected for reading based on title and abstract.

III. Granulomatous and Lymphocytic Interstitial Lung Disease

i. Historical background

The term “Granulomatous-Lymphocytic Interstitial Lung Disease” or “GLILD” was coined by Bates et al. in 2004 and resulted from the observation of coexistence of several coexistent histopathological patterns, with various granulomatous and lymphoproliferative features found in lung biopsies of CVID patients. [5]

Lymphocytic interstitial pneumonia (LIP) and follicular bronchitis/bronchiolitis are the lymphoproliferative patterns commonly found in lung biopsy of CVID associated GLILD patients. In 1973 Liebow and Carrington first described LIP in four patients with hypogammaglobulinemia. [17] and, as no further investigation was undertaken to understand the hypogammaglobulinemia, a connection with extra-salivary lymphoproliferative involvement of Sjögren’s syndrome was proposed at the time. [17] The histological lesion of follicular bronchiolitis/bronchitis found on lung biopsy in a CVID patient was originally reported in 1985 by Yousem et al. [18] The first association with autoimmune disorders was reported in a CVID patient with LIP and pernicious anemia by Levinson et al. in 1976. [19]

Historically, several authors described the presence of granulomas in the lungs, lymph nodes and other organs of CVID patients. [20] According to the authors, the description of granulomas varied between “sarcoid”, “sarcoid-like” or simply “granulomas” . [20] The presence of multisystemic noncaseating granulomas led some authors to consider the diagnosis of sarcoidosis associated to CVID. [21, 22] The first case report of “CVID associated-sarcoidosis” was described by Bronsky and Dunn in 1965 on a 37 year old woman. [23]

Reflecting this controversy, Mechanic et al. highlighted the impairment of T-cell response to pathogens and their possible implication in granuloma formation in CVID patients with granulomatous disease, as well as its higher morbidity in contrast with the classic presentation of sarcoidosis. [20]

Recently diffuse pulmonary disease with similar characteristics as described in GLILD have been reported in other immunodeficiencies. GLILD is known to potentially complicate the X-linked inhibitor of apoptosis (XIAP) deficiency. This is a primary immunodeficiency characterized by Epstein-Barr virus (EBV)-driven hemophagocytic lymphohistiocytosis (HLH), splenomegaly, and colitis.

A case report of patients with X-linked inhibitor of apoptosis suffering from GLILD presented reduced switched memory B cells, elevated transitional B cells and increase in the expression of $CD21_{low}CD38_{low}$ B cells. Lung biopsy showed non-necrotizing granulomas, cellular and follicular bronchitis and areas of organizing pneumonia. [24]

Recombination-activating gene (RAG) mutations are associated with a spectrum of clinical manifestations including atypical severe combined immunodeficiency (SCID) which is defined by the expansion of TCR $\gamma\delta_+$ T cells induced by a systemic cytomegalovirus infection and combining a immunodeficiency with granulomatous disease accompanied or not by autoimmune phenomena. A case report of a seven year old girl previously diagnosed with SCID developed GLILD with histopathological features of LIP and follicular bronchiolitis in lung biopsy. [25]

A few cases of Kabuki syndrome with biopsy-proven GLILD have also been reported. [26] Kabuki syndrome is commonly associated with low immunoglobulin levels with CVID-like features. An expansion of $CD21_{low}$ B cell and a reduced number or dysfunctional regulatory T cells are also oftenly found. [27] The diagnosis is made based on four out of five characteristics amongst distinctive facial features, skeletal and mental abnormalities. [26] Additionally, patients presenting with this syndrome have higher susceptibility to suffer from autoimmune disease and lymphoproliferative diseases such as B-cell NHL and Hodgkin lymphoma. [26]

Homozygous mutations in LRBA can induce an early onset of hypogammaglobulinemia and recurrent infections, autoimmune disease, chronic lung disease and gastrointestinal disorders. Deleterious LRBA mutations lead to dysfunctional B-cell differentiation and reduced autophagy. As LRBA-deficient EBV cells have also an increased susceptibility to apoptosis, the combination of reduced autophagy and increased apoptosis may play a role in the pathogenesis of autoimmune features related to LRBA deficiency.[28] A case report of a child with LRBA presenting with a diffuse parenchymal lung disease showing lymphocytic interstitial pneumonia and lymphoid follicular hyperplasia resembled histopathologic features of GLILD in lung biopsy. [28]

Several reports of patients harboring cytotoxic T lymphocyte associated protein 4 (CTLA-4) mutations presented lung lymphocytic infiltrates. CTLA-4, also known as CD152, represents a key player on the immunosurveillance inducing inhibitory effects on T cells. CTLA-4-deficient patients present a dysregulation in regulatory T cells, hyperactivation of effector T cells and a possible B cell lymphopenia with decreased expression of CTLA-4 in B cells and decreased frequencies of $CD27_+$ switched memory B cells.[29]

Two cases of GLILD have been reported in 22q11.2 deletion syndrome. This particular immunodeficiency is defined by a T cell lymphopenia due to a thymic hypoplasia and has also been associated with autoimmune disorders. [30] Two patients have been diagnosed with GLILD in Good's syndrome. Patients with Good's syndrome present classically thymoma with combined T and B cells immunodeficiency. [31]

A case of a boy under 1 year old with hypogammaglobulinemia of unclear etiology in infancy presented histopathological findings also consistent with GLILD in lung biopsy. [30]

ii. Physiopathology of GLILD

Although some mechanistic links have already been elucidated, the underlying pathogenesis of GLILD is still not yet fully understood. Granuloma formation in the lungs is generally found in response to microbial antigens and, consequently, opportunistic infectious agents in CVID patients may play a role in the pathogenesis of GLILD. [32] An impairment of lymphocyte proliferative response to antigens (candida albicans and tetanus toxoid) and mitogens (phytohemagglutinins, concavalin A, pokeweed) has been demonstrated in CVID patients. [20] Consequently, it has been suggested that a chronic intracellular microbial infection might initiate granulomatous lung formation. [33] According to some authors these findings support the theory that granuloma formation results from an anomalous sequestration of antigen due to a defective immune response such as dysfunctional T cells, abnormal cytosolic pathway or an altered cytokine serum profile. [20] However, necrotizing granulomas, as a result of an infectious lung disease, are rarely seen in CVID patients. [34] One case of a 12 years old girl reports the development of granulomatous and lymphoproliferative lung disease after a *Toxoplasma gondii* infection. [35] Unfortunately, granulomas are commonly of non-necrotizing nature in CVID patients [20, 32] and the presence of microorganism in histopathologic analysis of lung biopsy has not been verified systematically. [32]

One of the first proposed hypothesis was a lymphocyte proliferation possibly caused by a viral infection. An opportunistic infection by a γ-Herpes virus, Human-herpes virus type 8 (HHV8) - also known as Kaposi's sarcoma-associated herpesvirus - has been proposed since its involvement in lymphoproliferative diseases in secondary immunodeficiencies such as HIV-1 and organ transplant. [36] In a cohort study, the presence of HHSV8 genome was tested in CVID-patients with and without GLILD, in patients receiving intravenous γ-globulin and normal blood donors. Genomic DNA from this B cell lymphotropic virus obtained from peripheral blood mononuclear cells were screened by nested and real time-quantitative polymerase chain reaction (PCR). The presence of HHSV8 genome was confirmed in 6 out of 9 CVID patients with GLILD, 1 out of 21 CVID patients without GLILD and I none of the patients receiving intravenous γ-globulin or in normal blood donors. [36] Nonetheless, studies enrolling other CVID cohorts need to be performed to confirm the type of interaction between HHSV8, lymphocyte immunodeficiency and polymorphisms within the promoters of cytokine genes in the etiology of GLILD. [36, 37]

The involvement of the Epstein-Barr Virus (EBV), another γ-Herpes virus, well studied in infectious mononucleosis and Burkitt lymphoma, is questioned in the pathogenesis of GLILD and lymphocytic interstitial pneumonia (LIP). [38] This virus presents a similar tropism for B-cells inducing their transformation and proliferation in vitro. [38] In vivo studies have been conducted with two types of cellular infections: a productive infection associated with replicative forms in the oropharynx and a non-productive infection associated with latent forms in lymphocytes. [39] The latest is privileged in the hypothesis of lymphoid hyperactivity and lymphocytic infiltration. EBV genome was mostly detected in association with lymphomas occurring either in immunocompromised patients and in pediatric patients with LIP secondary to Acquired Immunodeficiency Syndrome (AIDS). [38] It remains controversial which lymphocyte is predominant in the lymphocytic infiltrate of LIP, as well as, the relevance of the dysregulation of B-lymphocytes and T-lymphocytes combined. The compromise of the immune system by the proliferation of infected B-cells and the impairment of the immunologic surveillance of the cytotoxic T cells over the infected B-cells may represent a vital factor for the EBV-induced B-cell proliferation. [38]

Furthermore, the component of T cell dysfunction in CVID patients is related with a reduced $CD4_+$ naïve T cells, especially $CD4_+$ $CD45RA_+$ $CCR7_+$.[10, 40] Giovanetti et al. correlated splenomegaly in CVID patients with a severe reduction of $CD4_+$ naïve T cells and a substantial T cell activation, proliferation and apoptosis. [11] Thus, an imbalance of secretion of cytokines was found among CVID patients in comparison with controls. Subsets of T cells, $CD4_+$ and $CD8_+$ secrete higher levels of IFN-γ (Interferon-γ) in patients with lower $CD4_+$ T cells counts. On the contrary, secretion of IL-10 by $CD4_+$ and $CD8_+$ subsets was lower in CVID patients than in controls. [11] In addition, a subgroup of CVID patients, defined as “Late Onset Common Immunodeficiency” (LOCID) and characterized by recurrent opportunistic infections and/or CD4 T cell count <200 x 10_6 cells/L showed a higher risk to develop splenomegaly and granulomatous disease. [40] Consequently, the higher prevalence of lymphoproliferative disorder in patients presenting lower $CD4_+$ T cell counts indicate a possible implication of a T cell defect in the pathogenesis of GLILD. [40]

An elevated circulating TNF levels and its receptor have also been reported in CVID patients presenting $CD4_+$ T cells depletion and splenomegaly. [41] Intrinsic variability in TNF production between individuals is mostly explained by inherited factors, hence Mullighan et al. intended to link genetic factors with clinical features by genotyping 6 biallelic single nucleotide polymorphisms in 350 individuals (150 CVID patients and 200 controls).

As a result, a significant correlation between TNF+448A allele and granulomas has been reported. [41, 42] Furthermore, clinical features (splenomegaly) and immunophenotyped peripheral blood cells ($CD3^+$ lymphopenia and $CD8^+CD57^+$ lymphocytosis) closely associated to granulomatous disease are also correlated with TNF+448A. [41]

Thereby Mullighan et al. hypothesized that underlying granuloma formation may be the result of an elevation of TNF levels caused by an abnormal lymphocyte activation. [41] Furthermore TNF plays an essential role in the maintenance of granulomas. [32] Studies of 13 genes in 163 CVID patients show the presence of *a-t-a* IL-10 promoter haplotype (-1082) in almost 80% of CVID patients with granulomatous disease compared to 42% of CVID patients without granulomatous disease. [42] Consequently, a possible interaction between TNF and IL-10 have been proposed. A reduced IL-10 serum levels due to the *a-t-a* IL-10 promoter haplotype located in the regulatory area IL-10 promoter might yield an increase secretion of TNF. [42]

iii. Clinical evaluation

Regarding respiratory complains, an exertional dyspnea is the predominant finding and can be associated with productive cough. [8] Chronic productive cough is frequently associated with the complications of recurrent respiratory infections, such as bronchiectasis. [5] Inspiratory crackles are occasionally audible during the pulmonary auscultation and splenomegaly is commonly revealed by ultrasound. [8, 10] The association of splenomegaly and lymphadenopathy is relatively frequent. [10] Moreover, digital clubbing can be observed during physical examination. [5]

Autoimmune manifestations are strongly associated with GLILD. Beside possible autoimmune cytopenia other autoimmune disorders can be present in these patients like pernicious anemia, autoimmune enteropathy, thyroiditis, vitiligo, arthritis and various connective tissue diseases [10]. As such, clinical manifestations of these diseases can also be present in GLILD patients.

iv. Laboratory features

Patients with CVID- related GLILD patients still encounter diagnostic criteria for CVID. Consequently, patients present low serum levels of IgG, IgA and possibly IgM. [3]In regard to immunoglobulin's titer, as the reference range varies according to age groups and ethnicity, it is important to define the lower limit of normal range according to the geographical region valid for the patient. [3]

Other haematologic parameters, such as leukopenia due to lymphopenia might be present. [43] Anemia and thrombocytopenia can also be found in CVID-related GLILD patients in the setting of autoimmune hemolytic anemia or immune thrombocytopenic purpura. [10]

As mentioned above, the unveiling of a lack of protective immune response by determining antibody titers after pneumococcal conjugates vaccination is essential in CVID patients. [3]

A retrospective study of 15 CVID patients suffering from ILD showed that progression of CVID related GLILD can be accompanied by distinct laboratory findings. Progressive lung disease was associated with lower mean immunoglobulin G levels, increases in IgM levels above 20 mg/L and a more significant thrombocytopenia. (44) In fact, all stable ILD patients maintained platelets counts above 80 $x10_3/\mu L$.[44]

Another study reported the finding of an elevated serum angiotensin-converting enzyme levels above the upper limit of normal in 14 out of 16 tested patients. [8]

Regarding lung physiology, a restrictive ventilatory defect associated to a low diffusing capacity for carbon monoxide (DLCO) is the common hallmark on pulmonary function tests (PFT) of CVID patients with GLILD. An obstructive ventilatory defect can be observed when associated to bronchiectasis. It should be noted that some patients can present normal PFT [8], especially in the case of limited disease.

The bronchoalveolar lavage (BAL) is commonly used for a reliable exclusion of opportunistic lung infection and can also assure useful information from the differential counts of BAL cells. BAL profile is lymphocytic (lymphocyte ≥20 %) in 85% of patients with a reported mean lymphocyte count of 37.3% ± 15.3%. The CD4/CD8 T-cell ratio is <3,5 in approximately 90% of the subjects. with a mean value of 1.6 ± 1.1%. [8]

v. Radiological findings

CVID-associated GLILD may present chest radiograph abnormalities like with interstitial pattern resembling pulmonary fibrosis, multiple discrete nodules, peribronchial cuffing and bronchiectasis. Apart from nodules, all radiographic features have commonly a basal distribution. [45]

The evaluation of GLILD is frequently performed by high-resolution chest computed tomography (HRCT) because chest radiographic imaging is not significantly sensitive. [4] Although not consensual, the use of IV radiocontrast can be useful in the presence of mediastinal lymphadenopathies. The definition of radiological findings is commonly based on the Fleischner Society criteria. Thus, reticular pattern is described as fine, intermediate or coarse; nodule as round or oval opacity with less than 3 cm of diameter and smooth margins; architectural distortion as a misplacement of pulmonary bronchial, vascular, fissural or septal anatomy; ground-glass opacity as an increased attenuation of the lung with preservation of the bronchial and vascular markings; opacification as an homogenous attenuation without the preservation of the bronchial and vascular margins; traction bronchiectasis as an irreversible, frequently irregular, dilatation of a bronchi within areas of retractile pulmonary fibrosis. [46] Within the abnormalities found in HRCT in GLILD patients, coarse linear type of reticulation is more frequently found, with a predominance in the lower lobes. When present, architectural distortion is more frequent in the lower lobes and traction bronchiectasis are usually similarly distributed among the lung parenchyma. [6, 47] Nodules are frequently described and are similarly distributed among the lung parenchyma. Smaller nodules (<5mm) are usually well-defined and randomly distributed, contrarily to sarcoidosis. When larger nodules are present they tend to be ill-defined and bronchocentric. [47] However, some studies qualify the nodular pattern of GLILD as macronodular or scattered nodular disease in association with consolidation and ground glass predominantly in the lower lobes. [48]

The involvement of the lung is similar between genders. Nodular and reticular manifestations are usually found simultaneously. [47] (Fig.1) A group of British clinicians considered that the presence of solid or subsolid nodules, pure ground glass opacification and hilar and/or mediastinal lymph node enlargement is highly suggestive of GLILD in CVID patients. [4]

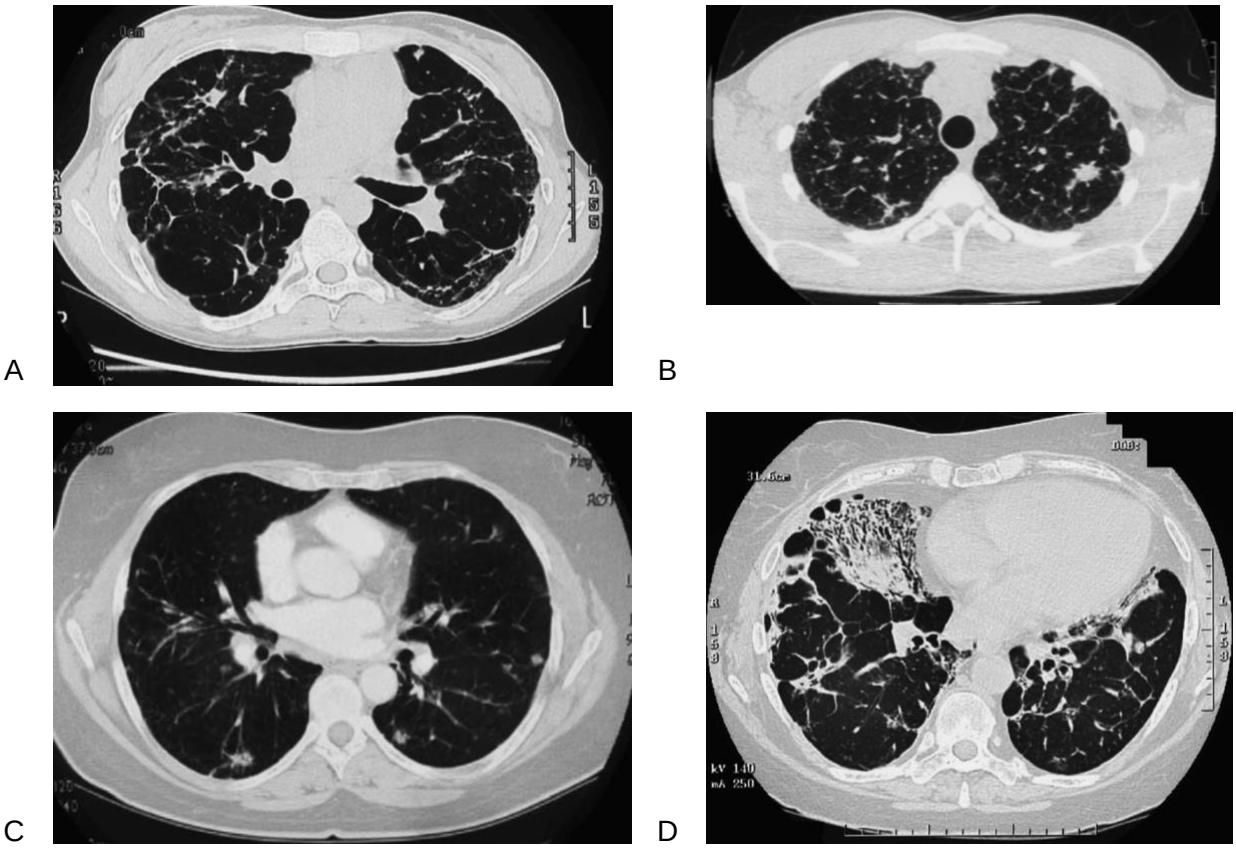

Figure 1 High resolution CT in CVID patient

A) Bilateral coarse reticulation B) Coarse reticulation in association with ill-defined nodules C) Small, well-defined and randomly distributed nodules and larger, ill-defined, bronchocentric nodules in same patient D) **Reticulation and traction b**ronchiectasis. Adapted from Park et al.[47]

Some studies have used the Bhalla scoring system, originally established for cystic fibrosis, to evaluate the progression and extent of the pulmonary changes in CVID, whether GLILD-related or not [45, 49] The original scoring system classifies a normal HRCT with 25 points. The severity and extension of bronchiectasis, peribronchial thickening, mucus plugging, sacculations, abscesses, emphysema, bullae, the number of generations of bronchial divisions affected and the presence of consolidation or collapse are subtracted from 25. [50] For any criteria, if no parenchymal or bronchial changes are detected in chest imaging no points are attributed. [50] As the assessment of nodules was not originally contemplated, two other parenchymal parameters were added to evaluate the total number and size of nodules. The evaluation from the modified Bhalla score ranged from 0 to 29 points. [49] (Table 2). Currently there are no accepted radiologic scores strictly for GLILD.

Table 2. Modified Bhalla score

Category	0	1	2	3
Bronchiectasis severity	Absent	Mild (luminal diameter slightly greater than the diameter of adjacent vessel)	Moderate (luminal diameter 2 to 3 times the diameter of adjacent vessel)	Severe (luminal diameter > 3 times the diameter of adjacent vessel)
Peribronchial thickening	Absent	Mild (airwall thickness equal to the diameter of adjacent vessel)	Moderate (airwall thickening ≤2 times the diameter of adjacent vessel)	Severe (airwall thickening > 2 times the diameter of adjacent vessel)
Bronchiectasis extent *	Absent	1-5	6-9	>9
Extent of mucus plugging*	Absent	1-5	6-9	>9
Abscesses/ vesiculations*	Absent	1-5	6-9	>9
Bronchial generations affected (bronchiectasis/mucus)	Absent	>4th GE	>5th GE	>6th GE
Number of bullae	Absent	Unilateral	Bilateral	>4
Emphysema extent*	Absent	1-5	>5	
Collapse/consolidation	Absent	Subsegmentary	Segmentary/lobar	
Number of nodules	Absent	1-4	>4	
Size of nodules	Absent	< 1cm	>1cm	

*Bronchopulmonary segments; GE: Generation
Adapted from Milito et al. and Bhalla et al. [49, 50]

The timing for radiological screening of CVID patients mainly for the presence of GLILD, is no consensual. Some authors recommend biannual screening of CVID patients with an active autoimmune disease or other non-infectious inflammatory disease, patients with recurrent lower respiratory tract infections and patients with significant structural airway disease or interstitial lung disease in HRCT. However, some authors defend HRCT screening once every five years as adequate. [51] This five-year serial CT imaging monitorization is questioned since the critical progression of GLILD, hence the adequate timing for treatment initiation, may be missed. [48]

The use of F18-FDG PET-CT (2-[(18)F]-fluoro-2-deoxy-d-glucose positron emission tomography and computed tomography) as a combined imaging modality to assess both anatomical and metabolic abnormalities is considered of great interest. The progression and extent of the lymphoproliferative condition may be assessed even if structural changes in conventional imaging techniques (CT or MRI) are not significantly altered and, therefore, potentially missed. [48] (Fig.3)

Concerns have been raised about the risk associated with CVID patient's exposure to radiation along with the higher radio sensitivity of CVID patients and a life-time follow-up. [49] Milito et al. proposed an alternative to radiation, assessing pulmonary changes with magnetic resonance imaging (MRI). A comparison between MRI and HRCT found a high concordance rate in the identification and scoring of bronchiectasis severity, extent of bronchiectasis, mucus plugging, number and size of nodules, emphysema and consolidation. (Fig. 2) Nonetheless, HRCT remains superior to detect the involvement of distal bronchial generation, specially up to the fifth generation. In MRI, the diffusion weighted imaging sequences (DWI) identifies areas of active inflammation and was proposed as a marker of disease activity, helping advanced disease management by distinguishing areas of active disease from chronic lung disease.[49]

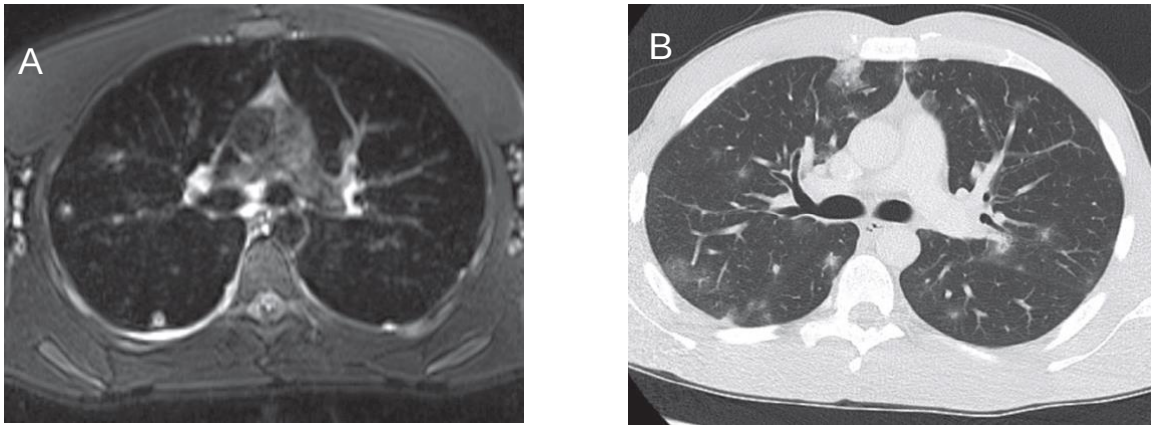

Figure 2 Comparison of MR and CT images from a patient with CVID-related GLILD

MRI (A) provides less spatial resolution; however, these T2-weighted images show the presence of edema (high signal) within some nodules. The CT image (B) shows bilateral ground-glass appearance and more dense nodular infiltration, only some of which is visible on MRI. Adapted from Verma et al. [6]

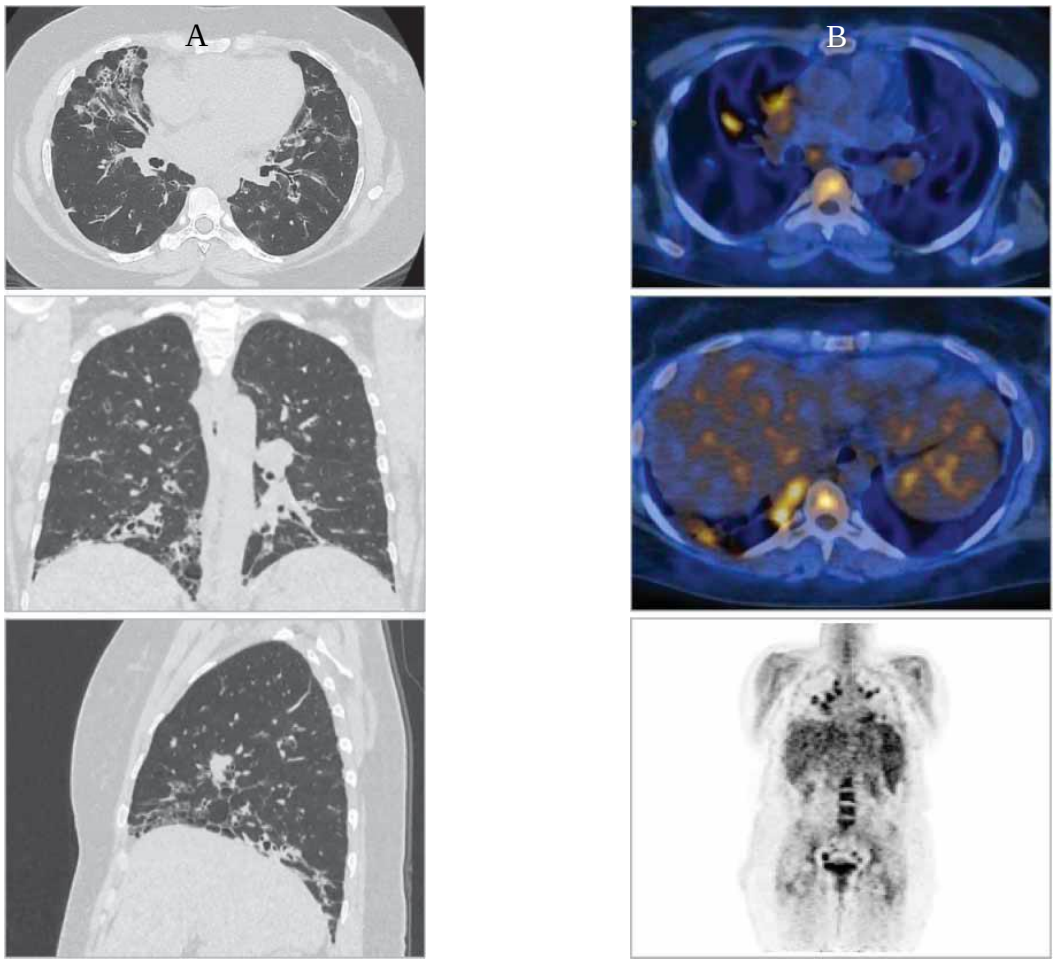

Figure 3 HRCT and PET/CT findings in a CVID patient GLILD

A) High-resolution computed tomography: axial, coronal and sagittal views show several nodules with peri-lymphatic distribution without predominance in the upper lobes, and the co-existence of bronchiectasis.

B) PET-CT findings shows hilar lymph nodes and peri-lymphatic nodules on FDG uptake, an inhomogeneous FDG uptake area of consolidation at the right lower lobe of the lung, and inhomogeneous liver and spleen FDG uptake with splenomegaly. Bone marrow activation images are also detectable. Bronchoalveolar lavage fluid cell analysis showed lymphocytosis (25%) with an increase in B-cells (73% were represented by CD21 low-activated B-cells). Lymphoproliferative disease was initially ruled out through trans-bronchial biopsy. Surgical lung biopsy examination was consistent with granulomatous-lymphocytic interstitial lung disease. Liver biopsy examination showed nodular lymphoid hyperplasia. Adapted from Cinetto et al. [52] Adapted from Cinetto et al. [52]

vi. Histopathology

In CVID-related GLILD patients there is typically presence of granulomas and peribronchiolar and interstitial CD4-cell predominant lymphocytic infiltration. [4, 53] The granulomatous inflammation is predominantly non-necrotizing and constituted of epithelioid histiocytes. The association with multinucleate giant cells is infrequent. [54] The distribution of granulomas within the lung parenchyma is nonlinear with the inflammatory infiltrate, appearing both, in association and far afield. Commonly, granulomas are present in the interstitium and along the bronchovascular bundles while less evident in the pulmonary alveolus. [54] The mature-appearing lymphocytes constitute the nodular peribronchial inflammation, which expend into a dense, nodular and diffuse inflammatory infiltrate within the interstitium. [54] Given the homogenous pattern of the lymphocytic infiltration, an isolated peribronchial or interstitial pattern is very uncommonly seen. [54] (Fig.4A)

As mentioned above, LIP and follicular bronchitis/bronchiolitis are the most prevalent histopathologic patterns in patients with CVID. [53] Other histopathologic features are also described such as lymphoid hyperplasia, organizing pneumonia and interstitial fibrosis.[54] The characteristic findings in LIP are the diffuse inflammatory infiltrates along the interstitium composed by mature-appearing lymphocytes, plasma cells and histiocytes. The presence of clusters of epithelioid histiocytes are uncommon. The follicular bronchiolitis pattern is characterized by bronchiolocentric lymphoid follicles with germinal center. Similar features are found in lymphoid hyperplasia: lymphoid follicles with germinal center but with a larger distribution, often established along the lymphatic system and interlobular septa. (Fig.4B) [5] The organizing pneumonia histological pattern is identified by Masson bodies which are fibroblastic nodules arranged in pale, myxoid stroma within the alveolar space and adjacent interstitium. These fibroblastic proliferations can be found around granulomas. [54] (Fig.5B). In GLILD the organizing pneumonia component, when present, is always intermixed with other patterns. Interstitial fibrosis is also reported in CVID-associated GLILD patients and it is composed by interstitial collagen deposits. In severe cases an architectural distortion of the alveolar septa and metaplastic epithelium associated to traction bronchiectasis may be seen. [54] (Fig.6)

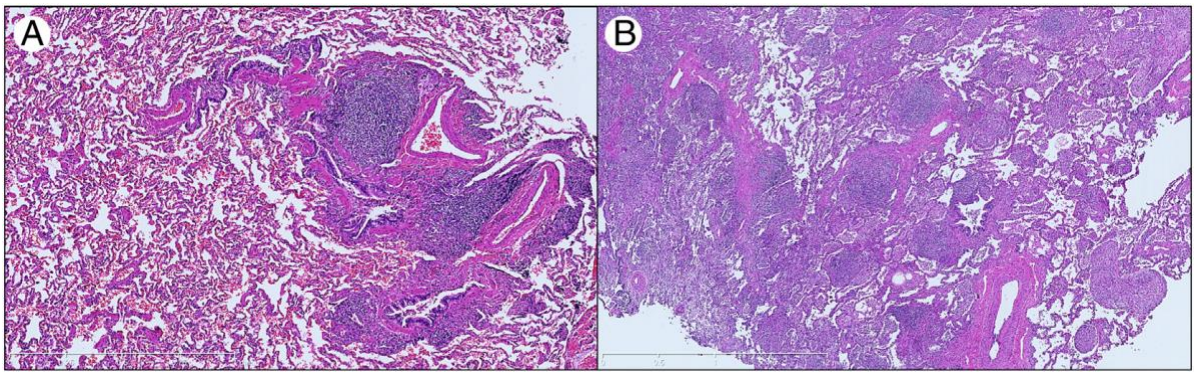

Figure 4 Peribronchiolar and interstitial lymphocytic infiltration in GLILD.

There are nodular lymphoid aggregates associated with bronchioles (A) and dense nodular, and diffuse interstitial lymphocytic infiltration (B). H&E, original magnification x 100. Adapted from Rao et al [54]

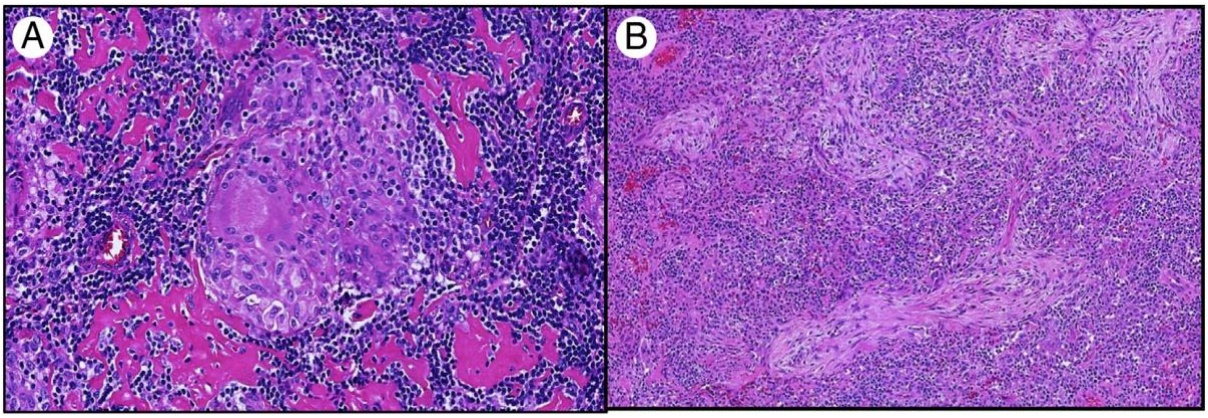

Figure 5 Granulomata and organizing pneumonia in GLILD.

A well-formed epithelioid cell granuloma (A) and organizing pneumonia characterized by prominent Masson bodies within airspaces (B). H&E, original magnification x200 (A) and x100 (B). Adapted from Rao et al [54]

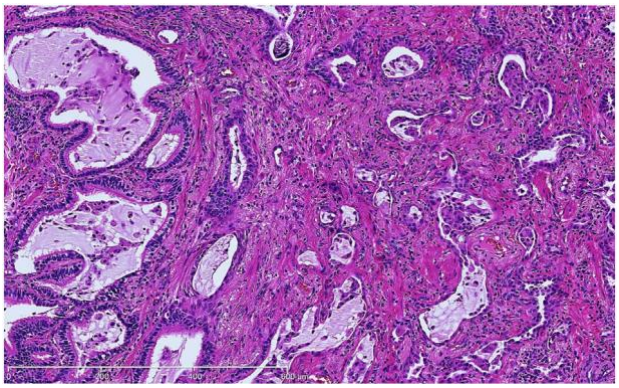

Figure 6 Interstitial fibrosis in GLILD.

There is expansile interstitial fibrosis with remodeled airspaces lined by metaplastic bronchiolar epithelium. H&E, original magnification x200. Adapted from Rao et al. [54]

As GLILD seems to represent the parenchymal lung expression of a multisystemic process, besides the lung, granulomas are commonly located in lymph nodes and spleen. However, other organ system locations have been detected, such as skin, spleen, bone marrow, brain, retina, small bowel and kidney. [32] The majority of patients (60%) with lung granulomas present granulomas in another organ. [32] This multisystemic involvement is frequently defined under the term of “granulomatous disease”. [32]

vii. Diagnostic criteria

GLILD should have an integrative multidisciplinary diagnosis. A recent change in clinical manifestations - mainly breathlessness and/or cough - can provide assistance to a diagnostic insight, even if it is not an invariable finding. Therefore, a high index of suspicion is crucial to diagnose GLILD in patients with CVID and, eventually other rare primary immunodeficiencies. [4]

Clinical features (splenomegaly and/or lymphadenopathy, AIHA or ITP) and laboratory findings (low Ig A levels and relative increase of $CD21^{low}$ B cells) have been suggested as predictive biological markers to identify subgroups of CVID patients at risk to develop GLILD. [43] A decrease of circulating $CD3^{+}$ and $CD8^{+}$ T cells counts in lymphocyte enumeration were also found predictive of GLILD in CVID patients. [5]

The presence of new abnormalities on HRCT are highly suggestive of GLILD although no radiological findings are specific enough to assure a definitive diagnosis by its own. Understandably, pulmonary infection represents an important differential diagnosis and it should be excluded through invasive microbiological testing performed by flexible bronchoscopy. [4]

Even sometimes presumably associated with multisystemic manifestations, the nature of the associated ILD cannot be accessed by extrapulmonary manifestations. [4] Video-assisted thoracoscopic surgical lung biopsy (VATS) generally allows for the exclusion of other differential diagnoses and a confident diagnosis of GLILD when typical histopathologic figures are present: granulomatous inflammation, peribronchial and interstitial lymphocytic infiltration with a $CD4^{+}$ cell predominance. [4]

The British consensus statement on CVID-related GLILD recommends the surgical lung biopsy to be stained for immunomarkers (CD3, CD4, CD8 and CD20), microorganisms such as *Mycobacteria,* fungi and also for clonality to discard the possibility of lymphoma. [4]. Viral markers for EBV and CMV should also be performed in the lung biopsy whenever possible. [4]

The workup of suspected GLILD patients should include other tests, particularly complete lung function tests (spirometry, lung volumes and gas-transfer) to assess the severity of the disease and to monitor the disease course and treatment response. [4] Molecular tests pursuing specific underlying genetic mutations LRBA/cytotoxic T lymphocyte associated protein 4 (CTLA-4) should be assessed if GLILD is diagnosed. [4]

viii. Differential diagnosis

Given the histopathological elements present in the lung of patients with GLILD, the main differential diagnosis needing a careful exclusion are protracted lung infections, sarcoidosis, hypersensitivity pneumonitis, organizing pneumonia and pulmonary lymphoma.

Even though IgG replacement is able to reduce susceptibility for severe infections, lower respiratory tract infections represent a priority differential to exclude. [4, 6] The main bacterial pathogens frequently involved are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*. [6, 55] The investigation for infection relies on microscopy and culture por bacteria, *Mycobacteria* and fungi on BAL. Further investigations including PCR for *Mycobacteria*, atypical bacteria, respiratory viruses and direct immunofluorescence for *Pneumocystis jiroveci* were not consensually considered essential to the investigation. [4]

In patients non previously diagnosed with CVID, the presence of non-caseating granulomas without signs of infection makes sarcoidosis a preferential differential diagnosis of GLILD. There is a high risk that a wrong diagnosis of sarcoidosis can be causing a significant delay until a correct diagnosis of CVID-related GLILD is made. Patient's mean age at diagnosis can be similar for both entities, with 43 ± 11,5 years of range for sarcoidosis and 44 ± 17 years of range for CVID associated GLILD. Even though, contrarily to GLILD a slight female predominance can be observed in sarcoidosis. [8] The association with recurrent pulmonary infections and autoimmune diseases is generally not present in sarcoidosis. Opposed to GLILD, a polyclonal hypergammaglobulinemia is frequently found in patients with sarcoidosis. [5] Frequent in GLILD, the presence of crackles at auscultation, splenomegaly and hepatomegaly at inspection are atypical during physical examination, although also possible in sarcoidosis. [8] Furthermore, the presence of extra-thoracic localizations is unusual. [8] Pulmonary function testing demonstrates a range of possible results as obstructive, restrictive ventilatory defects or neither.[8] Lung function measurements are likewise variable in GLILD. Patients with extensive ILD in HRCT might present normal values of PFT. [8, 56] Despite also having a lymphocytic predominant BAL profile, the CD4/CD8 T-cell ratio is frequently superior to 3,5 in sarcoidosis. [8] Regarding HRCT findings the presence of micronodules is more common in sarcoidosis, and their distribution is typically perilymphatic. [8] The other main HRCT features like ground glass and airspace consolidation, are similar with the exception of the "halo sign" which is less frequent in sarcoidosis than in CVID-related GLILD. [8] While the prevalence of mediastinal lymph nodes is similar, the involvement of symmetrical hilar lymph nodes is the most frequent manifestation observed in sarcoidosis. [8, 57]

Opposed to GLILD, the well-circumscribed micronodular pattern follows a perilymphatic distribution with a middle and upper lung predominance. [4, 47] The presence of bronchiectasis in sarcoidosis patient is infrequent. [8] Sarcoidosis shares the histological pattern of non-necrotizing granulomatous inflammation with GLILD. Nevertheless, granulomas are characterized by well-circumscribed epithelioid histiocytes and multinucleated giant cells associated with a few surrounding of lymphocytes in opposition to the variability of nodules margins (irregular to regular margins) present in GLILD and randomly distributed among the lung parenchyma. [4, 5, 47] Granuloma formation commonly occurs in a lymphatic distribution. [54] The prognosis for patients with sarcoidosis is generally favorable. A spontaneous recovery is observed in numerous patients within 3 years after diagnosis. [57] Recommended first line therapy consists of 30-40 mg/d of prednisolone for 4-12 weeks, gradually reduced until reaching a 10 to 20 mg/d maintenance dose for 6 to 12 months of overall therapy. [57] Pulmonary sarcoidosis treatment is started when a worsening of symptoms or pulmonary function test deterioration is acknowledged. Cardiac and neurological involvement as well as pulmonary failure secondary to lung fibrosis may be fatal for a substantial number (<5%) of patients with sarcoidosis. [57]

The incidence of malignancies is generally higher in immunocompromised patients. The most frequent malignancy in CVID patients is lymphoma. [58, 59] B cells extranodal non-Hodgkin lymphoma (NHL) is the most common type of lymphoma recognized in CVID patients. [59] A higher incidence in female subjects within 40-70 years old was reported. The association with Epstein-Barr virus infection was not proved. [60-62] Several cases of MALT lymphomas (*Mucosa-associated Lymphoid Tissue lymphomas*) - related or not to Helicobacter pylori - have been reported, as well as marginal zone lymphoma and T-cell-rich B-cell EBV-associated lymphoma. [58, 62] Occasionally, the presence of a pulmonary BALT (Bronchus-associated Lymphoid Tissue) lymphoma can be a differential diagnosis to consider in a CVID patient with diffuse lung disease. [63] It usually presents itself radiologically by multiple, bilateral or unilateral, ill-defined nodules or areas of consolidation containing air bronchograms on HRCT. [63, 64] The diagnosis is based on the immunophenotypic and molecular studies in a biopsy specimen (transbronchial lung biopsy, transbronchial criobiopsy, transthoracic CT guided lung biopsy or surgical lung biopsy).[58] The site for biopsy can be assisted by the analysis of lymphoid hyperactivity on a PET-CT scan. [58] Lymphoma in CVID patients has a poor outcome and represents the second cause of death after respiratory failure. [62]

As organizing pneumonia can also be a histological feature taking part of the histopathological array of findings in GLILD, limited bronchoscopic sampling in these patients showing organizing pneumonia as the only or predominant abnormality may result in a wrong clinical diagnosis of CVID-related OP. [54]

As stated, while the most common interstitial lung disease in patients with CVID is GLILD, other interstitial lung diseases such as OP - previously referred as Bronchiolitis Obliterans Organizing Pneumonia - has been reported in CVID patients. Clinical manifestations of OP are not specific (fatigue, mid dyspnea, fever and cough). [65, 66] At physical examination, sparse crackles may be found, however clubbing is infrequent. [65, 66] Thoracic imaging with HRCT presents multiple consolidations within an alveolar pattern, possibly migratory and preferentially bilateral and peripheral. [66] A restrictive ventilatory defect is commonly found in PFT. [66] BAL differential cell count may show an increase in neutrophils, eosinophils and especially lymphocytes. The ratio CD4/CD8 in OP is commonly decreased. It is noteworthy that few plasma cells and mastocytes can also be evidenced. [66] Diagnosis of OP is histopathological with the presence of buds of granulation tissue within alveolar spaces giving a distinctive “butterfly pattern” and possibly progressing to the bronchioles with luminal obstruction. In addition to the interstitial inflammation, when not affected by buds of granulation alveoli may be filled with foamy alveolar macrophages. [66] Biopsy specimens are retrieved preferentially by bronchoscopy or VATS. [66] Corticosteroids are the classical treatment of choice for cryptogenic or secondary OP with an excellent response.

ix. Management

The management of CVID-GLILD patients requires a multidisciplinary setting combining immunologists, chest physicians, radiologists, pathologists, nurse specialists, respiratory rehabilitation and psychological support if needed. [4]

Firstly, immunoglobulin replacement therapy should be initiated when IgG levels are reduced, particularly under 4 g/L. Serum IgG levels should be optimized before the start of other specific immunosuppressive therapy for GLILD. Ig replacement is frequently given as 200-400 mg/kg of intravenous immunoglobulin (IVIg) administered every 4-6 weeks. [67] Maglione et al. proposed a minimum serum IgG level of 700 mg/dL for CVID-related GLILD patients, however with 1000 mg/dL being the objective. Interestingly, the IVIg dose necessary to maintain IgG above 700 mg/dL is generally higher in patients with ILD. [44] Serum Ig levels should be remeasured during follow-up every 6 to 12 months.[4, 67] There are reports of improvements in lung function and partial improvements on imaging under exclusive immunoglobulin replacement therapy in CVID-related GLILD patients. [4, 68, 69]

Nevertheless, the partial improvement on imaging potentially attainable under exclusive IVIg therapy is considered insufficient to induce remission of GLILD [68] and, in fact, progressive GLILD has been observed in CVID patients receiving Ig replacement. Although more studies are needed to prove or refute the worsening of the disease solely under optimal Ig replacement. [6], there is no consensus whether an expectant management following optimization of Ig levels is an acceptable strategy. [4]

Specific treatment for GLILD should generally be started in patients with declining lung function (even if within the normal range), whether if symptomatic or not. There is no indication to start treatment if patients are asymptomatic and present stable normal lung function. [4]

First line therapy for CVID-related GLILD patients is corticosteroids, preferring oral prednisolone. The initial dose used in the literature ranged from 20 mg/d to 1 mg/kg/d [4] Some authors, based on clinical experience, favor a high initial dose (1mg/kg/d) until significant amelioration of radiological and lung function abnormalities and then a gradually reduction. [6] Treatment duration should follow-up an individualized decision. The use of prolonged steroid treatment implies the monitorization of corticosteroid-induced CD4 lymphopenia and pneumocystis prophylaxis. [61]

Since half of patients do not respond to corticosteroids, second-line therapy is needed, either in combination or not. [6] Notably, long-term treatment with corticosteroids as monotherapy before the initiation of second line agents contributed to a less effective treatment response to immunosuppressors. [70] In stable disease, the need for maintenance therapy and the favored maintenance therapy are not well established. [4] The outcome of CVID-related GLILD patients may depend on the time of diagnosis, the effectiveness of the treatment regimen and to its time-related response. [70] The most used second-line agents have been azathioprine, rituximab and mycophenolate mofetil. [4] A combination of agents has been tried with success in patients with CVID-related GLILD. The combination of azathioprine with rituximab was chosen in several case series for their combined effects on T and B cells, respectively. The selection of this combo is based on the minor treatment response observed when these drugs were administered as single agents and on the rational for of combined pathogenetic role of B cells and T cells on GLILD. [56, 70] Besides pulmonary improvement, an improvement of splenomegaly was especially noticed in patients with transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) mutation. [56]

Other agents reported as potentially useful are anti-TNF agents, ciclosporin, hydroxychloroquine, methotrexate and tacrolimus. [4] The use of sirolimus, an mTOR inhibitor, affects effector T cells and may cause a diminution of lymphocyte's survival. Its efficacy was proven in monogenic immune disorder, CTLA-4 deficiency and autoimmune lymphoproliferative disorders. A higher expression of CTLA-4 by regulatory T cells after the use of sirolimus suggests an amelioration of T cells functions. [27] Furthermore specific genetic mutations such as CTLA-4 haploinsufficiency and LRBA defects may present severe complications and better disease control is achieved with Abatacept. [27] Genetic testing might be important to guide treatment [27], hence further research is needed to support biopsy at a single time point as a guide for future second-line therapy. [4, 27]

Importantly, an antimicrobial prophylaxis for *Pneumocystis jiroveci*, with co-trimoxazole, should be assured if CD4 lymphocyte count falls to less than $200x10_9$ cells/L. [6] Otherwise, experiences with azithromycin given as general antimicrobial prophylaxis presented no significant evidence of beneficial effects. [4, 6] Beside *Pneumocystis jiroveci*, other opportunistic infections have been reported in immunocompromised patients with GLILD, which include non-tuberculous *Mycobacteria*, cytomegalovirus, varicella zoster and one case of possible progressive multifocal leukoencephalopathy. [4]

Evaluation of treatment response can be assessed through modification of symptoms and exercise capacity, lung functions trends and comparison of serial HRCT. [4]

The first assessment of treatment response should occur at 6-12 weeks after the initiation of therapy and should preferentially encompass a gas transfer determination. An improvement of 20% in DL_{CO} and/or K_{CO} is considered significant. [4] HRCT comparative examination is generally performed 5-7 months after treatment initiation. [4] The use of PET-CT to evaluate treatment response enables an accurate non-invasive assessment of the improvement of disease activity, which is more sensitive than structural improvements. [48] (Fig. 7) The ideal interval for monitorization has not been established but a periodic assessment of every 4 to 5 months is considered adequate. In case of relapse no consensus was found for the benefit of repeating lung biopsy. [4]

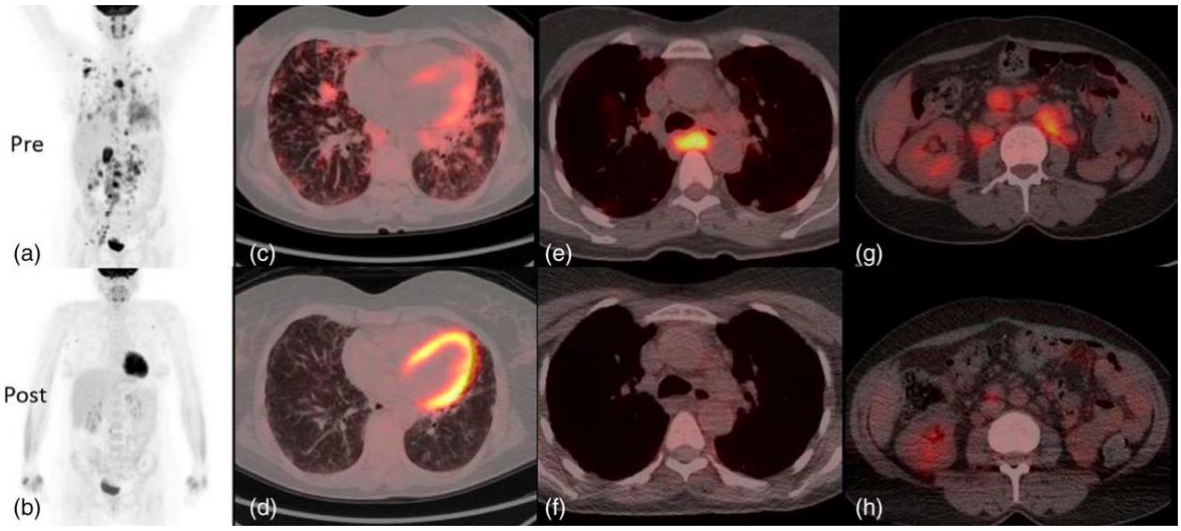

Figure 7 FDG PET-CT pre- and 3 months post-rituximab and mycophenolate treatment.
Whole body images pretreatment showing widespread abnormal uptake of tracer in the lung parenchyma and lymph nodes above and below the diaphragm (a). MIP images following treatment show near resolution of all the areas of abnormal tracer uptake (b).(c,d) Axial fused PET/CT images at the mid-thoracic level. The level of FDG uptake is represented by the intensity of color superimposed upon the CT image. Post-treatment images at the same level shows improvement of the nodularity with near resolution of abnormal FDG uptake within them (d). Images at the level of the carina show an enlarged lymph node exhibiting intense abnormal FDG uptake prior to treatment (e). Following treatment, the lymph node at this site normalizes in size and shows no abnormal tracer uptake (f). Pretreatment images through the abdomen at the level of the right renal hilum demonstrate numerous enlarged FDG avid retroperitoneal lymph nodes (g) which reduce in size and FDG uptake following treatment (h). Adapted from Jolles et al. [48]

Lung transplantation can be attempted in patients with respiratory failure due to severe progressive GLILD not responsive to medical treatment. [62] The results are variable and, although good post-transplant outcome has been reported [71], surgical complications or recurrence of ILD with respiratory failure have been reported within 30 months after transplant. [72] A an antithymocyte globulin can be used to induce immunosuppression and a multidrug approach composed by prednisolone, azathioprine and cyclosporin can be used to maintain immunosuppression. [73, 74] The anti-proliferative effect of mycophenolate mofetil on B cells may compromise life-threatening infection control. [73] Nonetheless, the optimal post-transplant immunosuppressive treatment and Ig replacement therapy regimen in transplanted patients with primary immunodeficiency warrant better clarification by new clinical studies. [73] It remains uncertain if the phenotypic heterogeneity between patients with CVID can explain the different transplantation outcomes. [73]

Further investigations, like the ongoing observational “Study of Interstitial Lung Disease in Primary Antibody Disease” (STILPAD) may provide new strategies of management and therapy for GLILD patients.

x. Prognosis

Firstly, the diagnosis of GLILD is associated to a poor outcome in CVID patients. [1] In a retrospective study of 69 patients, a significant reduction of 50% (13,7 years) in median survival was noted in patients with GLILD when compared to the median survival of nearly 30 years (28,8 years) in patients without GLILD. [5] (Fig. 8) Other retrospective studies also confirmed a reduced survival of CVID patients suffering from GLILD, in one of them with 30% of dead's resulting from severe restrictive lung disease/respiratory failure. [8, 20]

In CVID-related GLILD patients the leading causes of death are respiratory failure, lymphoma, solid malignancies and infections [32, 62] These findings support the hypothesis that optimal Ig replacement therapy and specific therapy (corticosteroids and immunosuppressive agents) might prevent the extensive ILD and granulomatous disease progression. [8]

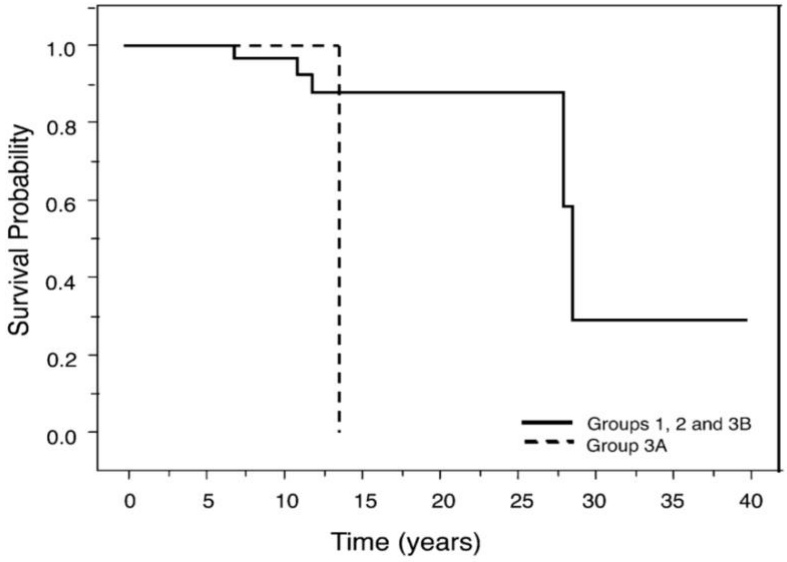

Figure 8 Kaplan-Meier survival plot between 2 groups of patients (GLILD vs non-GLILD).

Group 1: Patients without evidence of clinically significant lung disease

Group 2: Patients presenting chronic respiratory symptoms without diffuse radiographic lung abnormalities

Group 3: Patients presenting chronic respiratory symptoms with diffuse radiographic lung abnormalities and histological confirmation of GLILD (A) or another ILD (B)

The median survival of 28.8 years in groups 1, 2, and 3B (solid line) is compared with the median survival of 13.7 years in group 3A (dashed line; $P < .001$). There is no statistical difference in survival between groups 1, 2, and 3B. Time is from the date of CVID diagnosis. Adapted from Bates et al.[5]

IV. Conclusion

GLILD is an ILD commonly found in CVID patients and has been also reported in other primary immunodeficiencies. Its diagnosis has profound implications as, within patients with CVID complications, GLILD is significantly associated with increased mortality. An early detection of GLILD is likely to lead to an optimized management and possibly to improved long-term outcomes. Despite an increasing interest in ILD in the setting of primary immunodeficiencies, GLILD remains a type of ILD scarcely known throw the medical community, hence requiring greater awareness.

As discussed in this review, the unveiling of GLILD diagnosis is often a challenge to clinicians, demanding careful clinical reasoning and appropriate investigations. Major causes of noninfectious granulomatous lung disease compose the main differential diagnosis, mainly, sarcoidosis and lymphoma. Reliable biomarkers of disease endorsing screening, diagnosis and monitoring for progression in GLILD represent, undoubtedly, a key research priority.

Management of GLILD has been undertaken on a basis of small retrospective clinical trials and case reports. Drug selection has been based in IVIg replacement therapy and a first line therapy with prednisolone. Among the second-line agents, the azathioprine - rituximab combination has been predominantly advocated. Ongoing observational studies and further prospective studies might highlight the optimal timing and drug selection for treatment initiation and maintenance therapy, as well as its long-term impact on morbidity and mortality in this subgroup of CVID patients. In the light of the above, the complex decision-making process and the lack of prospective studies to guide management practice strongly suggest that management decisions should be attained in a multidisciplinary framework.

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