GRANULOMATOUS AND LYMPHOCYTIC INTERSTITIAL LUNG DISEASE

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Summary:

Granulomatous lymphocytic interstitial lung disease (GLILD) is a rare non-infectious complication affecting patients with common variable immunodeficiency disorders (CVID). Although the pathophysiology is not fully understood, it likely involves autoimmune dysregulation. GLILD usually occurs together with other non-infectious complications, raising morbidity and mortality. Symptoms are cough and dyspnoea but some patients remain asymptomatic. The clinical picture includes nodules, interlobular septal thickening, ground glass opacity and splenomegaly on imaging. Lung function varies between patients but is typically restrictive with decreased gas transfer. Excluding malignancy and infection is necessary as these may cause similar clinical presentations. Lung biopsy could be performed to confirm the diagnosis. GLILD usually appears as mixed histologic patterns, including lymphoid interstitial pneumonitis, follicular bronchiolitis, lymphoid hyperplasia, organizing pneumonia, and non-necrotizing granuloma. Optimizing immunoglobulin replacement therapy (IgRT) is essential before initiating treatment. Glucocorticoids remain the recommended first-line therapy however relapse usually occurs on dose-tapering and second-line immunosuppressants are recommended.

Take-home message: no more than 256 characters

- GLILD is a rare lung manifestation affecting 10-20% of people living with CVID. It is difficult to diagnose and manage. We encourage further cooperation in research to improve patient care and treatment.

Introduction

Lung complications are a leading cause of poor quality of life and decreased life expectancy in people living with Common Variable Immunodeficiency Disorders (CVID). CVID affects 1:50,000 –1:25,000 and is the most common symptomatic antibody deficiency (1). CVID is characterized by decreased levels of serum IgG, IgA and/or IgM with poor response to vaccines (2). The common immune defect among these patients is B-cell dysfunction. Defects in T cell function have been reported in one-third of patients (3). However, the cause of these defects remains unclear. Patients can be phenotyped into two groups; a group with recurrent infections only and a group with additional non-infectious complications. Optimizing immunoglobulin replacement therapy (IgRT) has significantly reduced infection rate, however, it does not affect the development of autoimmune and inflammatory conditions (4, 5). The more challenging complications in CVID patients are therefore the non-infectious complications (1, 6). This includes splenomegaly, autoimmunity, lymphoproliferative disorders, malignancy, and granulomatous infiltrations of lungs, lymph nodes and other organs (7).

The pulmonary manifestation in CVID may also be divided into two groups. Recurrent upper and lower airway infections are usually caused by encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumonia*. These frequent infections may lead to the development of bronchiectasis (8, 9). In contrast, systemic immune dysregulation is thought to be related to the development of interstitial lung disease (ILD) in CVID (CVID-related ILD, CVIDrILD, also known as granulomatous and lymphocytic interstitial lung disease, GLILD). CVIDrILD is a rare lung manifestation that occurs in 8 to 20% of CVID patients in conjunction with other non-infectious complications raising morbidity and mortality in these patients (10, 11). The purpose of this chapter is to review and describe the existing evidence on the diagnosis and management of CVIDrILD/GLILD.

Term and definition

The term GLILD was initially coined in 2004 by Bates et al. when they used it to describe CVID patients with histologic patterns of granulomata and lymphocytic infiltrates (12). Later, the term was used to describe patients with different pathological processes and even in the absence of granuloma, which makes the terminology confusing (13). A consensus definition by the British Lung Foundation and United Kingdom Primary Immunodeficiency Network (BLF/UKPIN) on what constitutes GLILD concluded GLILD is "a distinct clinico-radio-pathological ILD occurring in patients with CVID, associated with a lymphocytic infiltrate and/or granuloma in the lung, and in whom other conditions have been considered and where possible excluded (14)." The definition notes that GLILD is likely the lung manifestation of systemic immune dysregulation. Although GLILD was initially reported in CVID, studies later also identified it in immunodeficiency associated with specific genetic mutations. It has been reported in patients with CTLA-4 haploinsufficiency, LRBA deficiency, X-linked inhibitor of apoptosis (XIAP), RAG mutations, 22q11.2DS, and Good's syndrome (15-22). This may suggest the need for further consensus on what comprises GLILD. The term GLILD will be used in this chapter as synonymous with CVIDrILD.

Diagnosis of GLILD:

The diagnosis of GLILD is a challenge due to the heterogeneity of the disease and its unknown natural history. The lung manifestations share clinical, radiological, and histological characteristics with other conditions. According to BLF/UKPIN, whilst CT abnormalities can raise suspicion of GLILD, the presence of histopathological abnormalities on lung biopsy is still required to definitively confirm the diagnosis (14). Other cases might best be considered as having 'probable GLILD'. Thus, GLILD is a diagnosis of exclusion that persists after excluding other possible differential diagnoses such as malignancy and lymphoma. The diagnosis of GLILD relies on clinical, radiological, and histopathological features.

Clinical features

The most common symptoms are chronic cough and dyspnoea, especially with exertion. However, patients can be asymptomatic. This indicates the need for screening of patients with CVID to help detect GLILD and allow early intervention. The extrapulmonary involvement of granulomatous or inflammatory disease affects other organs such as the gastrointestinal tract, spleen, liver and lymph nodes (23) and patients with these complications and immune cytopaenias are at higher risk of GLILD. There is no relationship between gender, age, ethnicity, and GLILD development (24). In addition, smoking and obesity are not reported to be risk factors for developing GLILD (25).

Pulmonary function testing (PFT)

PFTs provides essential information for monitoring and evaluating treatment response in GLILD. PFT results vary between patients from a normal pattern, despite the abnormal changes in CT, to severe restriction with decreased gas transfer (10, 26, 27). Reduction in gas transfer could be an early sign of GLILD. It is therefore recommended to obtain spirometry and gas transfer at the time of CVID diagnosis as a baseline, with annual follow-up monitoring (28).

Radiology

Diagnostic imaging is an essential tool in detecting lung diseases. In addition to changes in symptoms and lung function, imaging may also assess the response to treatment. Chest x-ray is not sufficiently sensitive, whereas High-Resolution Computed Tomography (HRCT) is considered to be the gold standard for assessing lung changes in GLILD. CT findings include ill-defined large nodules (>5mm) and micronodules (<5mm), which predominantly affect the peribronchovascular and lower lobes with varying density. Air bronchograms and halo sign (ground glass opacity surrounding a pulmonary nodule), bronchial wall thickening, interlobular septal thickening, consolidation, hilar and/or mediastinal lymphadenopathy and splenomegaly are also reported in GLILD **(Figure 1)** (27, 29-31). In order to standardise HRCT scores, Meerburg et al. evaluated two radiologic scores developed for CVID in patients with GLILD. The Hartmann score appeared more valuable for longitudinal monitoring in that it considered more detail than the Baumann score (32).

Figure 1: CT image shows bilateral nodules with a ground-glass halo from patient with GLILD.

The use of fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) may be a useful assessment and monitoring tool in evaluating disease activity and treatment response in patients with GLILD (33). Fraz et al. reported that active pulmonary inflammation and progressive disease can be reflected by the increase in the mean standardised uptake value (SUVmean) when comparing patients with progressive GLILD to stable patients (34).

Given the benefit of HRCT, patients with lung complications related to CVID often undergo several radiological follow-up scans throughout their lives. Radiosensitivity in a small number of patients with CVID has been reported and repeated radiation exposure may have contributed to the increase in malignancy (35, 36). Thus, risk-benefit assessment should be taken into consideration before considering HRCT, such as lower dose protocols or considering an alternative approach such as Magnetic Resonance Imaging (MRI). MRI was reported to be reliable and non-inferior to HRCT in detecting bronchial and parenchymal abnormalities in GLILD. However, HRCT had higher sensitivity to identifying peripheral airway abnormalities (37, 38).

Histopathology:

Abnormality in lung imaging alone does not confirm the diagnosis of GLILD since these changes are indistinguishable from other pathologies. For this reason, biopsy of lung tissue has been suggested (39). The type of biopsy needed depends on evaluating risk, size and location of the lesion. Bronchoscopy with bronchoalveolar lavage (BAL) is usually performed first to exclude bacterial, fungal, and viral infections, and malignancy, with or without transbronchial biopsy although the yield for the latter is low. The need for surgical lung biopsy is raised when tissue is insufficient or there is a need for a definitive histopathological diagnosis. Video-assisted thorascopic surgery (VATS) is more widely performed than open lung biopsy due to fewer complications (40). Recently, transbronchial lung cryobiopsy (TBLC) was described in two case reports as a less invasive approach to the diagnosis of GLILD (41, 42).

Histologic findings of GLILD are usually described by mixed patterns, including lymphoid interstitial pneumonitis, follicular bronchiolitis, lymphoid hyperplasia, organizing pneumonia, and non-necrotizing granuloma **(Figure 2)** (13, 43). GLILD shares some histological and radiological features with sarcoidosis, and lymphoma leading to misleading or delayed diagnoses (39, 44). Sarcoidosis is typically associated with hyper- not hypogammablobulinaemia. Excluding primary immunodeficiency and precise clinical and radiological assessment are important to distinguish between these conditions.

Figure 2: Histology of granulomatous-lymphocytic interstitial lung disease showing a polymorphous infiltrate of lymphocytes, plasma cells, and macrophages High (A) and low (B) power photomicrographs of a VATS lung biopsy from a patient with CVID and GLILD. From reference 42 with permission.

Lung pathology in GLILD is heterogeneous and poorly understood. GLILD can be seen in patients with CVID in the absence of bronchiectasis or pneumonia; this supports the assumption that GLILD is likely related to immunological dysregulation (45). Lymphoproliferation in some patients has been related to the human herpesvirus 8 (46). However, there is no evidence supporting the relation between CMV or EBV viral or bacterial infection and inflammatory complications in these patients (47, 48). Low serum IgA level, low switched memory B cells and marginal zone B cells, expansion of CD21low B cells, lower CD3, CD4, and CD8 T cell counts have all been identified as a predictor of GLILD in patients with CVID (25, 27, 49).

Several studies have investigated the features of peripheral blood lymphocyte or BAL fluid in patients with GLILD. In a comparison of BAL fluid, Friedmann et al. found that those with GLILD have higher percentage of B cells mostly consisting of $CD21^{low}$ B cell, low regulatory T cells, and high T follicular helper (T_{FH})-like memory mostly composed of TH1 cells than patients with sarcoidosis (50). Maglione et al. describe the B cell hyperplasia that develops tertiary lymphoid structures and is driven by B cell-activating factor (BAFF) as the key pathogenic feature of GLILD. They reported a higher level of BAFF and serum IgM in CVID patients with progressive ILD (51). In contrast, Fraz et al. recently reported that BAFF was not significantly higher in their GLILD group and found that the levels of its soluble (s) receptor form (sBCMA) were significantly higher compared to patients with other non-infectious complications or infections only (52). They also found increased levels of T cell activation, pulmonary epithelial cell injury, and ECM remodelling markers. Their results were also consistent with Van Stigt et al. who reported a high level of the soluble form of the interleukin-2 receptor (sIL-2R or sCD25) in ten patients with GLILD compared to CVID patients with infection only and in patients with the progressive disease compared to stable (53).

Prediction models:

GLILD usually occurs in conjunction with other autoimmune complications, including splenomegaly, adenopathy, thrombocytopenia, autoimmune hemolytic anemia (AIHA), polyarthritis, hepatitis, and inflammatory bowel disease (12, 25, 27, 30, 49). Splenomegaly, along with AIHA and thrombocytopenia, were identified as possible risk factors for the development of GLILD. Three studies developed predictive models for GLILD based on clinical, laboratory, and/or radiological findings. Hartono et al. reported that a history of autoimmune hemolytic anemia (AIHA) and/or immune thrombocytopenia (ITP), splenomegaly, IgA levels less than 13 mg/dl, and CD21-low B lymphocytes greater than 5% of total CD21 B cells are predictive of GLILD in CVID with a ROC curve of 0.86(25). Cinetto et al. suggested similar models but added low gas transfer as a functional measure which increased the area under the ROC curve to 0.98 (27). The most recent model by Cabanero et al. found that lymphadenopathies, splenomegaly, a reduced number of CD8 cells, and a high Baumann's GLILD composite score predicts the presence of GLILD with a ROC curve of 0.985 (54).

Treatment of GLILD

The underlying mechanisms of GLILD are poorly understood, contributing to challenges managing this disease. Heterogeneity between studies regarding the optimal treatment for GLILD still exists due to a lack of evidence-based guidelines on how and when to treat patients.

Immunoglobulin replacement therapy (IgRT) should be optimised in all individuals with GLILD in order to maintain normal serum IgG levels (55, 56). Antimicrobial prophylaxis can help to reduce infections but does not appear to stop the progression of the disease (57).

Additional treatment is required in cases of disease progression. A consensus about when to commence treatment by BLF/UKPINnet was based on changes in symptoms and lung function. They recommended starting treatment in symptomatic patients with normal or abnormal but declining lung function, and asymptomatic patients with normal but declining lung function (**Figure 3**). Thus, deterioration in symptoms, progression on HRCT, or decreasing lung function are the main indications to initiate treatment (56). The selection of a therapy is influenced by a variety of factors such as efficacy, cost, and availability of the drug, patients' opinion, and risk and benefit assessment.

Figure 3: Simplified algorithm depicting GLILD treatment strategies.

Glucocorticoids such as prednisone with a maximum dose of 0.1-1.0 mg/kg/day are generally suggested as first-line treatment (56). However, there is variability in the clinical response to these. Lamers et al., in a systematic review on the efficacy of treatments of GLILD, emphasised that 57% of patients treated with glucocorticoids failed to induce remission (58). In contrast, Van Stigt et al. in their systematic review that evaluated the treatment efficacy on granulomatous disease in CVID patients reported that steroid monotherapy induces remission in 67% of patients with pulmonary granulomatous disease (59). In addition to different inclusion criteria, the main difference between the studies was how they defined remission. Lamers et al. considered remission as relapse-free improvement, while Van Stigt et al. reported remission when there was an improvement in symptoms, imaging, and/or lung function. Additional treatment can be considered as maintenance therapy to avoid the side-effects of long-term oral corticosteroids. Bintalib et al. recently reported that the use of MMF as second-line treatment was linked to long-term efficacy and allowed corticosteroid weaning in patients with GLILD and that watchful waiting was associated with progressive lung function decline (60).

Second-line immunosuppressive agents such as Azathioprine, Mycophenolate Mofetil (MMF), Rituximab, Methotrexate, Cyclosporine, and Infliximab have been suggested when treatment fails to induce remission, or when steroids cause problematic side effects (39). Of note, those agents have also been used in some as first-line treatment which reflects the heterogeneity between studies.

Rituximab is a monoclonal antibody that binds to CD20 molecules and depletes B-cells. The efficacy of rituximab as monotherapy has been reported in case studies (61-63). Rituximab in combination with mycophenolate or azathioprine was reported to be effective in treating patients with GLILD (51, 64). Verbsky et al. reported a longitudinal retrospective analysis of 39 patients with GLILD who were treated with a combination of Rituximab with either Azathioprine or MMF with the histologic findings of B cells and T cells in the lung (64). They found an improvement in HRCT and spirometry but not gas exchange in 75% of patients and reported relapse in only 9 patients.

In patients with LRBA and CTLA-4 deficiency, Abatacept has efficacy for lung disease, as well as other complications, (15, 16). The efficacy of using this in patients with GLILD was reported by Von Spe-Mayer and colleagues in a pilot study. They reported complete remission in 5 out of 10 GLILD patients with significant radiological and the lung function improvement (65). No relapse was reported which could be due to the short follow-up period.

Hemopoietic stem cell therapy (HSCT) is a therapeutic intervention used in patients with severe CVID, generally when there is a specific genetic mutation identified. Outcomes in surviving patients were reassuring but the mortality rate related to the procedure is still high (28, 66). Evidence for HSCT to treat GLILD has been limited and survival rates vary between 48% to 70% (58). This could be related to many factors including the severity of the disease, other organ involvement, and infection.

The controversy about the optimal treatment of GLILD prevails in the literature. The main limitations of studies that focus on treatment are the small sample size and retrospective design. Thus, a need for Randomised Control Trials (RCT) is imperative to standardise management. The results of a large multi-centre observational study of Interstitial Lung Disease in Primary Antibody Deficiency (STILPAD) is awaited and will shed further light on efficacy of the available treatment options. A prioritisation exercise in GLILD addressed and prioritised unanswered research questions (67). The top questions were about optimal treatment to induce and maintain remission, when to initiate treatment, and what diagnostic approach could help detect GLILD in CVID (67). This indicates the urgent need for further research to understand the underlying pathophysiology of GLILD to allow appropriate treatment.

Conclusion:

GLILD is associated with reduced survival in patients with CVID. As a result, early detection and ongoing follow-up are essential. HRCT and pulmonary function testing is the preferred monitoring approach. The decision to initiate treatment relies on close monitoring. Finally, controversy regarding optimal treatment still exists, and RCTs are required.

Conflict of interest/disclosure information for each author:

- Conflict of interest: H.M. Bintalib has nothing to disclose.
- Conflict of interest: SOB has received grant support from CSL Behring and personal fees or travel expenses from Immunodeficiency Canada/IAACI, CSL Behring, Glaxo SmithKline, Baxalta US Inc and Biotest.
- Conflict of interest: JRH has received support to attend meetings, personal payment and payment to his employer from companies that make medicines to treat respiratory disease and immunoglobulin products.

References:

1. Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650-7.
2. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2016;4(1):38-59.
3. Saikia B, Gupta S. Common Variable Immunodeficiency. The Indian Journal of Pediatrics. 2016;83(4):338-44.
4. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: a review of evidence. Journal of Allergy and Clinical Immunology. 2017;139(3):S1-S46.
5. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol. 2002;109(6):1001-4.
6. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112(2):277-86.
7. Maglione PJ, Overbey JR, Cunningham-Rundles C. Progression of Common Variable Immunodeficiency Interstitial Lung Disease Accompanies Distinct Pulmonary and Laboratory Findings. Journal of Allergy and Clinical Immunology: In Practice. 2015;3(6):941-50.
8. Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46(10):1547-54.
9. Sperlich JM, Grimbacher B, Soetedjo V, Workman S, Burns SO, Lowe DM, et al. Predictive Factors for and Complications of Bronchiectasis in Common Variable Immunodeficiency Disorders. J Clin Immunol. 2022;42(3):572-81.
10. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. Journal of Allergy and Clinical Immunology. 2004;114(2):415-21.
11. Odnoletkova I, Kindle G, Quinti I, Grimbacher B, Knerr V, Gathmann B, et al. The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society for Immunodeficiency (ESID) registry data. Orphanet Journal of Rare Diseases. 2018;13(1):201.
12. Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol.114(2):415-21.
13. Dhalla F, Lochlainn DJM, Chapel H, Patel SY. Histology of Interstitial Lung Disease in Common Variable Immune Deficiency. Front Immunol. 2020;11:605187.
14. Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. Journal of Allergy and Clinical Immunology: In Practice. 2017;5:938-45.
15. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. AUTOIMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science. 2015;349(6246):436-40.
16. Schwab C, Gabrysch A, Olbrich P, Patino V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. Journal of Allergy and Clinical Immunology. 2018;142(6):1932-46.

17. Lopez-Herrera G, Tampella G, Pan-Hammarstrom Q, Herholz P, Trujillo-Vargas CM, Phadwal K, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. Am J Hum Genet. 2012;90(6):986-1001.
18. Steele CL, Dore M, Ammann S, Loughrey M, Montero A, Burns SO, et al. X-linked Inhibitor of Apoptosis Complicated by Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) and Granulomatous Hepatitis. J Clin Immunol. 2016;36(7):733-8.
19. Buchbinder D, Baker R, Lee YN, Ravell J, Zhang Y, McElwee J, et al. Identification of Patients with RAG Mutations Previously Diagnosed with Common Variable Immunodeficiency Disorders. Journal of Clinical Immunology. 2015;35(2):119-24.
20. Mather MW, Hayhurst H, Bacon CM, Cole TS, Pan-Hammarstrom Q, Misbah S, et al. Mutation of TNFRSF13B in a child with 22q11 deletion syndrome associated with granulomatous lymphoproliferation. J Allergy Clin Immunol. 2015;135(2):559-61.
21. Sood AK, Funkhouser W, Handly B, Weston B, Wu EY. Granulomatous-Lymphocytic Interstitial Lung Disease in 22q11.2 Deletion Syndrome: a Case Report and Literature Review. Curr Allergy Asthma Rep. 2018;18(3):14.
22. Jensen ML, Bendstrup E, Hilberg O. Granulomatous-lymphocytic interstitial lung disease and recurrent sinopulmonary infections in a patient with Good's syndrome. BMJ Case Reports. 2015;30:30.
23. Cinetto F, Scarpa R, Rattazzi M, Agostini C. The broad spectrum of lung diseases in primary antibody deficiencies. Eur Respir Rev. 2018;27(149).
24. Boursiquot JN, Gerard L, Malphettes M, Fieschi C, Galicier L, Boutboul D, et al. Granulomatous disease in CVID: retrospective analysis of clinical characteristics and treatment efficacy in a cohort of 59 patients. J Clin Immunol. 2013;33(1):84-95.
25. Hartono S, Motosue MS, Khan S, Rodriguez V, Iyer VN, Divekar R, et al. Predictors of granulomatous lymphocytic interstitial lung disease in common variable immunodeficiency. Annals of Allergy, Asthma and Immunology. 2017;118(5):614-20.
26. Lopez AL, Paolini MV, Fernandez Romero DS. Lung disease in patients with common variable immunodeficiency. Allergol Immunopathol (Madr). 2020;48(6):720-8.
27. Cinetto F, Scarpa R, Carrabba M, Firinu D, Lougaris V, Buso H, et al. Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) in Common Variable Immunodeficiency (CVID): A Multicenter Retrospective Study of Patients From Italian PID Referral Centers. Frontiers in Immunology. 2021;12 (no pagination).
28. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): common variable immunodeficiency disorders. The Journal of Allergy and Clinical Immunology: In Practice. 2016;4(1):38-59.
29. Bouvry D, Mouthon L, Brillet PY, Kambouchner M, Ducroix JP, Cottin V, et al. Granulomatosis-associated common variable immunodeficiency disorder: a case-control study versus sarcoidosis. Eur Respir J. 2013;41(1):115-22.
30. Mannina A, Chung JH, Swigris JJ, Solomon JJ, Huie TJ, Yunt ZX, et al. Clinical predictors of a diagnosis of common variable immunodeficiency-related granulomatous-lymphocytic interstitial lung disease. Annals of the American Thoracic Society. 2016;13(7):1042-9.
31. Tanaka N, Kim JS, Bates CA, Brown KK, Cool CD, Newell JD, et al. Lung diseases in patients with common variable immunodeficiency: Chest radiographic, and computed tomographic findings. Journal of Computer Assisted Tomography. 2006;30(5):828-38.
32. Meerburg JJ, Hartmann IJC, Goldacker S, Baumann U, Uhlmann A, Andrinopoulou ER, et al. Analysis of Granulomatous Lymphocytic Interstitial Lung Disease Using Two Scoring Systems for Computed Tomography Scans-A Retrospective Cohort Study. Frontiers in Immunology. 2020;11:589148.
33. Jolles S, Carne E, Brouns M, El-Shanawany T, Williams P, Marshall C, et al. FDG PET-CT imaging of therapeutic response in granulomatous lymphocytic interstitial lung disease (GLILD) in

common variable immunodeficiency (CVID). Clinical and Experimental Immunology. 2017;187(1):138-45.
34. Fraz MSA, Moe N, Revheim ME, Stavrinou ML, Durheim MT, Nordoy I, et al. Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency-Features of CT and ¹⁸F-FDG Positron Emission Tomography/CT in Clinically Progressive Disease. Frontiers in Immunology. 2020;11 (no pagination).
35. Aghamohammadi A, Moin M, Kouhi A, Mohagheghi MA, Shirazi A, Rezaei N, et al. Chromosomal radiosensitivity in patients with common variable immunodeficiency. Immunobiology. 2008;213(5):447-54.
36. Mahmoodi M, Abolhassani H, Mozdarani H, Rezaei N, Azizi G, Yazdani R, et al. In vitro chromosomal radiosensitivity in patients with common variable immunodeficiency. Cent Eur J Immunol. 2018;43(2):155-61.
37. Arslan S, Poyraz N, Ucar R, Yesildag M, Yesildag A, Caliskaner AZ. Magnetic resonance imaging may be a valuable radiation-free technique for lung pathologies in patients with primary immunodeficiency. Journal of clinical immunology. 2016;36(1):66-72.
38. Milito C, Pulvirenti F, Serra G, Valente M, Pesce AM, Granata G, et al. Lung magnetic resonance imaging with diffusion weighted imaging provides regional structural as well as functional information without radiation exposure in primary antibody deficiencies. J Clin Immunol. 2015;35(5):491-500.
39. Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2017;5(4):938-45.
40. Sigurdsson MI, Isaksson HJ, Gudmundsson G, Gudbjartsson T. Diagnostic surgical lung biopsies for suspected interstitial lung diseases: a retrospective study. The Annals of thoracic surgery. 2009;88(1):227-32.
41. Doan J, Rao N, Kurman JS, Routes JM, Benn BS. Granulomatous and lymphocytic interstitial lung disease diagnosed by transbronchial lung cryobiopsy. Cryobiology. 2020;97:231-4.
42. Sasaki J, Tominaga M, Sudou M, Tokisawa S, Nishii Y, Zaizen Y, et al. Granulomatous Lymphocytic Interstitial Lung Disease in Multiple Myeloma. Internal Medicine. 2022:9758-22.
43. Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. The Lancet Respiratory Medicine. 2015;3(8):651-60.
44. Verbsky JW, Routes JM. Sarcoidosis and common variable immunodeficiency: similarities and differences. Semin Respir Crit Care Med. 2014;35(3):330-5.
45. Maglione PJ, Overbey JR, Radigan L, Bagiella E, Cunningham-Rundles C. Pulmonary radiologic findings in common variable immunodeficiency: clinical and immunological correlations. Ann Allergy Asthma Immunol. 2014;113(4):452-9.
46. Wheat WH, Cool CD, Morimoto Y, Rai PR, Kirkpatrick CH, Lindenbaum BA, et al. Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. J Exp Med. 2005;202(4):479-84.
47. Maglione PJ, Ko HM, Beasley MB, Strauchen JA, Cunningham-Rundles C. Tertiary lymphoid neogenesis is a component of pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;133(2):535-42.
48. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol. 2009;145(6):709-27.
49. Lopes JP, Ho HE, Cunningham-Rundles C. Interstitial Lung Disease in Common Variable Immunodeficiency. Frontiers in Immunology. 2021;12 (no pagination).
50. Friedmann D, Unger S, Keller B, Rakhmanov M, Goldacker S, Zissel G, et al. Bronchoalveolar Lavage Fluid Reflects a T<inf>H</inf>1-CD21^{low} B-Cell Interaction in CVID-Related Interstitial Lung Disease. Frontiers in Immunology. 2021;11.

51. Maglione PJ, Gyimesi G, Cols M, Radigan L, Ko HM, Weinberger T, et al. BAFF-driven B cell hyperplasia underlies lung disease in common variable immunodeficiency. JCI Insight. 2019;4(5).
52. Fraz MSA, Michelsen AE, Moe N, Aaløkken TM, Macpherson ME, Nordøy I, et al. Raised Serum Markers of T Cell Activation and Exhaustion in Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency. Journal of clinical immunology. 2022:1-11.
53. van Stigt AC, Dalm VASH, Nagtzaam NMA, van Rijswijk DA, Barendregt BH, van Hagen PM, et al. Soluble Interleukin-2 Receptor Is a Promising Serum Biomarker for Granulomatous Disease in Common Variable Immune Deficiency. Journal of Clinical Immunology. 2021;41(3):694-7.
54. Cabanero-Navalon MD, Garcia-Bustos V, Forero-Naranjo LF, Baettig-Arriagada EJ, Nunez-Beltran M, Canada-Martinez AJ, et al. Integrating Clinics, Laboratory, and Imaging for the Diagnosis of Common Variable Immunodeficiency-Related Granulomatous-Lymphocytic Interstitial Lung Disease. Frontiers in Immunology.13.
55. Hasegawa M, Sakai F, Okabayashi A, Sato A, Yokohori N, Katsura H, et al. Intravenous Immunoglobulin Monotherapy for Granulomatous Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency. Intern Med.56(21):2899-902.
56. Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract. 2017

5(4):938-45.
57. Hasegawa M, Sakai F, Okabayashi A, Sato A, Yokohori N, Katsura H, et al. Intravenous immunoglobulin monotherapy for granulomatous lymphocytic interstitial lung disease in common variable immunodeficiency. Internal Medicine. 2017;56(21):2899-902.
58. Lamers OA, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm VA, et al. Treatment strategies for GLILD in common variable immunodeficiency: a systematic review. Frontiers in immunology. 2021;12:1205.
59. van Stigt AC, Dik WA, Kamphuis LS, Smits BM, van Montfrans JM, van Hagen PM, et al. What Works When Treating Granulomatous Disease in Genetically Undefined CVID? A Systematic Review. Frontiers in immunology. 2020;11:606389.
60. Bintalib HM, Lowe DM, Mancuso G, Gkrepi G, Seneviratne SL, Burns SO, et al. Corticosteroid-induced remission and mycophenolate maintenance therapy in granulomatous lymphocytic interstitial lung disease: long-term, longitudinal change in lung function in a single-centre cohort. ERJ Open Res. 2022;8(4).
61. Cereser L, De Carli R, Girometti R, De Pellegrin A, Reccardini F, Frossi B, et al. Efficacy of rituximab as a single-agent therapy for the treatment of granulomatous and lymphocytic interstitial lung disease in patients with common variable immunodeficiency. J Allergy Clin Immunol Pract.7(3):1055-7.e2.
62. Ng J, Wright K, Alvarez M, Hunninghake GM, Wesemann DR. Rituximab Monotherapy for Common Variable Immune Deficiency-Associated Granulomatous-Lymphocytic Interstitial Lung Disease. Chest.155(5):e117-e21.
63. Tessarin G, Bondioni MP, Rossi S, Palumbo L, Soresina A, Badolato R, et al. Rituximab as a Single Agent for Granulomatous Lymphocytic Interstitial Lung Disease in Common Variable Immune Deficiency. J Investig Allergol Clin Immunol.29(6):470-1.
64. Verbsky JW, Hintermeyer MK, Simpson PM, Feng M, Barbeau J, Rao N, et al. Rituximab and antimetabolite treatment of granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency. J Allergy Clin Immunol. 2021;147(2):704-12 e17.
65. von Spee-Mayer C, Echternach C, Agarwal P, Gutenberger S, Soetedjo V, Goldacker S, et al. Abatacept use is associated with steroid dose reduction and improvement in fatigue and CD4-dysregulation in CVID patients with interstitial lung disease. The Journal of Allergy and Clinical Immunology: In Practice. 2021;9(2):760-70. e10.

66. Wehr C, Gennery AR, Lindemans C, Schulz A, Hoenig M, Marks R, et al. Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency. J Allergy Clin Immunol. 2015;135(4):988-97 e6.
67. Hurst JR, Abbas SH, Bintalib HM, Alfaro TM, Baumann U, Burns SO, et al. Granulomatous–lymphocytic interstitial lung disease: an international research prioritisation. ERJ open research. 2021;7(4).