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Tomographic aspects of common variable immunodeficiency suggestive of lymphocytic granulomatous interstitial lung disease: a systematic review

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Systematic review

ABSTRACT

Objective: Common variable immunodeficiency (CVID) is a primary antibody deficiency characterised by hypogammaglobulinemia, leading to the occurrence of infections and at times, the development of diffuse lesions with granulomatous characteristics and lymphoproliferative histopathological patterns. Granulomatous lymphocytic interstitial lung disease (GLILD) is a rare form of interstitial lung disease where imaging exams play a crucial role, therefore this article aims to assess the prevalence of tomographic findings and evaluate whether bronchiolitis and ground glass opacity are suggestive findings for the diagnosis of GLILD in patients with CVID without a previous GLILD diagnosis. **Method:** a systematic review using the prisma methodology was conducted with five descriptors across four databases, covering publications from 2012 to 2022 in the portuguese, english, and spanish languages. **Results:** out of 234 initial results, 26 articles were included, representing a total of 775 analysed CVID patients. Various radiographic abnormalities were identified, with notable findings including bronchiectasis, pneumonia, atelectasis, among others. **Conclusion:** the results indicate that it is not possible to establish a pattern of tomographic findings, demonstrating the heterogeneity in the presentation of glild.

Keywords: Common variable immunodeficiency; Lung diseases, interstitial; Bronchiolitis; Tomography, x ray computed

Aspectos tomográficos da Imunodeficiência Comum Variável sugestivos do diagnóstico de Doença Pulmonar Intersticial Linfocítica Granulomatosa: uma revisão sistemática

Resumo

Introdução: A Imunodeficiência Comum Variável é uma deficiência primária de anticorpos, que se caracteriza pela hipogamaglobulinemia, o que propicia o surgimento de infecções e, por vezes, o desenvolvimento de lesões difusas de características granulomatosas e padrões histopatológicos linfoproliferativos. A doença pulmonar intersticial linfocítica granulomatosa (GLILD) é uma forma rara de doença pulmonar intersticial, em que os exames de imagens são de grande importância, porém, não há achados típicos que possam sugerir o diagnóstico conclusivo da doença granulomatosa. **Método:** Revisão sistemática realizada com cinco descritores em quatro bases de dados, de publicações entre 2012 a 2022, nos idiomas português, inglês e espanhol. **Resultados:** A partir de 234 resultados iniciais, 26 artigos foram incluídos, o que equivale a um total de 775 pacientes com CVID analisados. Sendo identificada diversas alterações radiográficas com alguma anormalidade, destacando-se os achados de bronquiectasia, pneumonia, atelectasias, entre outros. **Conclusão:** Os resultados mostraram que não se é possível traçar um padrão dos achados tomográficos encontrados, demonstrando a heterogenidade de apresentação da GLILD.
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Palavras-chave: Imunodeficiência de Variável Comum; Doença Pulmonar Intersticial Linfocítica Granulomatosa; Bronquiolite; Tomografia Computadorizada;
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INTRODUCTION

Common Variable Immunodeficiency (CVID) is a primary antibody deficiency characterised by low levels of IgG, IgA, and/or IgM in the blood, along with normal or reduced values of B and/or T lymphocytes. This leads to the development of chronic or recurrent infections, primarily affecting the respiratory and gastrointestinal tracts[1].

The pathophysiology of CVID is not fully understood, but in many patients, it may result from intrinsic defects in B cells, particularly memory B cells (CD27+), which have been associated with certain clinical aspects of the disease. Elevated levels of memory B cells with persistent IgM (CD27+IgM+) appear to correlate with the presence of infections, while reduced classical memory B cells are associated with low levels of IgG and the occurrence of autoimmunity[2].

CVID can manifest in various ways, affecting individuals of all ages, and its aetiology often remains unknown. Its worldwide prevalence is approximately 1:25.000-50.000 people, with a higher prevalence in individuals of northern European descent. Regarding age, there are two peaks in terms of age: one in the first 10 years of life, and another in the early 30s, with no distinct gender preference[3].

The main clinical manifestations of CVID include acute, chronic, or recurrent infections of the respiratory and gastrointestinal tracts, such as pneumonia, bronchitis, sinusitis, ulcerative colitis, Crohn's disease, among others. There is a higher susceptibility to infections by enteroviruses and typical viral or fungal agents of opportunistic infections, even in the presence of seemingly intact cellular immunity[3].

Additionally, CVID is characterised by an association with autoimmune diseases, with 20% of cases linked to conditions such as hemolytic anaemia, idiopathic thrombocytopenic purpura, rheumatoid arthritis, and pernicious anaemia. There is also an increased incidence of malignancies, with an elevated risk of non-Hodgkin lymphoma and gastric cancer documented[4,5].

In cases of recurrent lung and sinus infections, the main symptoms include dyspnea, copious sputum production, hemoptysis, cough, chest pain, wheezing, sinus pressure, chills, and/or lymphadenopathy. Progression can lead to bronchiectasis, a condition characterised by permanent and abnormal dilation of the bronchi, resulting in the inability to adequately clear mucus and other secretions. However, although the

infectious pulmonary complications of CVID are well described, there are reports of patients developing diffuse lesions with granulomatous characteristics and lymphoproliferative histopathological patterns, grouped under the name Granulomatous Lymphocytic Interstitial Lung Disease (GLILD).

GLILD is a rare form of interstitial lung disease (ILD) involving the presence of granulomas and lymphocytic infiltrates in the lung interstitium in patients with CVID[6]. The exact causes of GLILD are not fully understood, and the disease can manifest variably in different patients. In diagnosis, clinical evaluation and a series of tests are necessary for a proper assessment, with lung biopsy being the only conclusive diagnostic method. However, imaging tests, typically Chest Computed Tomography, pulmonary function assessment, used to evaluate progression and treatment response, and examinations such as flexible bronchoscopy to exclude infections and perform surgical lung biopsy for conclusive diagnosis, are consensus requirements[6].

According to the consensus of the British Thoracic Society published in 2017, tomography findings are used more for the exclusion of differential diagnoses such as infections, lymphoma, and sarcoidosis than for GLILD confirmation. However, some pulmonary findings were recurrent at the time of diagnosis, including the presence of solid and semi-solid nodules, ground-glass opacities, thoracic lymph node (hilar and/or mediastinal) dilation, and splenomegaly. The presence of bronchiectasis, honeycombing, cysts, and consolidations is less common[6,7].

Therefore, this article consists of a literature review in medical databases with the aim of verifying the prevalence of tomographic findings observed in the 2017 British consensus, and evaluating whether bronchiolitis and ground glass opacity were suggestive findings for the diagnosis of GLILD in patients with CVID without a previous GLILD diagnosis.

METHODS

Research was conducted in the PubMed, Virtual Health Library (BVS), Scielo, and Trip Medical Database for original articles on the prevalence of tomographic findings, with a focus on bronchiolitis and ground glass opacity in patients with Common Variable Immunodeficiency (CVID), published from January 2012 to December 2022. The aim was

to investigate whether there was a significant number of articles justifying the findings and suggesting the diagnosis of Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) in CVID patients without a previous GLILD diagnosis. The systematic review was organised based on the CoCoPop protocol[8], which assesses Condition, Context, and Population. The condition corresponded to the prevalence of bronchiolitis and ground glass opacity, the context to imaging exams, and the population observed in the articles filtered through inclusion and exclusion criteria.

Included were articles described as case reports, cohort studies, or clinical trials that presented images or reports of radiological and/or chest computed tomography (CT-chest) findings. The descriptors used in the databases were: Bronchiolitis, Common variable immunodeficiency or CVID, Ground glass, and Tomography, X-Ray Computed, with the following search string: ("computed tomography") and ("common variable immunodeficiency" or "CVID") and bronchiolitis and ground glass. The descriptors were chosen in English as the ones in Portuguese did not yield results in the search.

All articles not written in English, Spanish, or Portuguese were disregarded. Additionally, the exclusion criteria included: absence of lung findings; absence of figures or reports of chest radiography or CT-chest exams; grey literature; lack of association with CVID; and incomplete text. Systematic review articles were also excluded, as they had not been peer-reviewed.

Two independent researchers selected the articles in the databases following the PRISMA Statement recommendations[9], which advocate for four stages: identification, selection, eligibility, and inclusion. In all stages, inclusion and exclusion criteria were applied.

The selection stage comprised phases: 1 - reading titles; 2 - reading abstracts; 3 - reading the complete article. Following PRISMA recommendations, articles were selected by reading title and checking for correlation with the proposed objective, resulting in the identification of 234 articles of which 89 remained after duplicate detection. These articles proceeded to the eligibility stage through reading of the abstract, with 55 being excluded for deviating from the topic. Finally, of the 34 articles not discarded, on complete paper reading (Figure 1), 26 articles remained eligible. Data extracted from these articles were descriptively summarised and presented in tables

and graphs. Meta-analysis was not performed due to a lack of sufficient quantitative data.

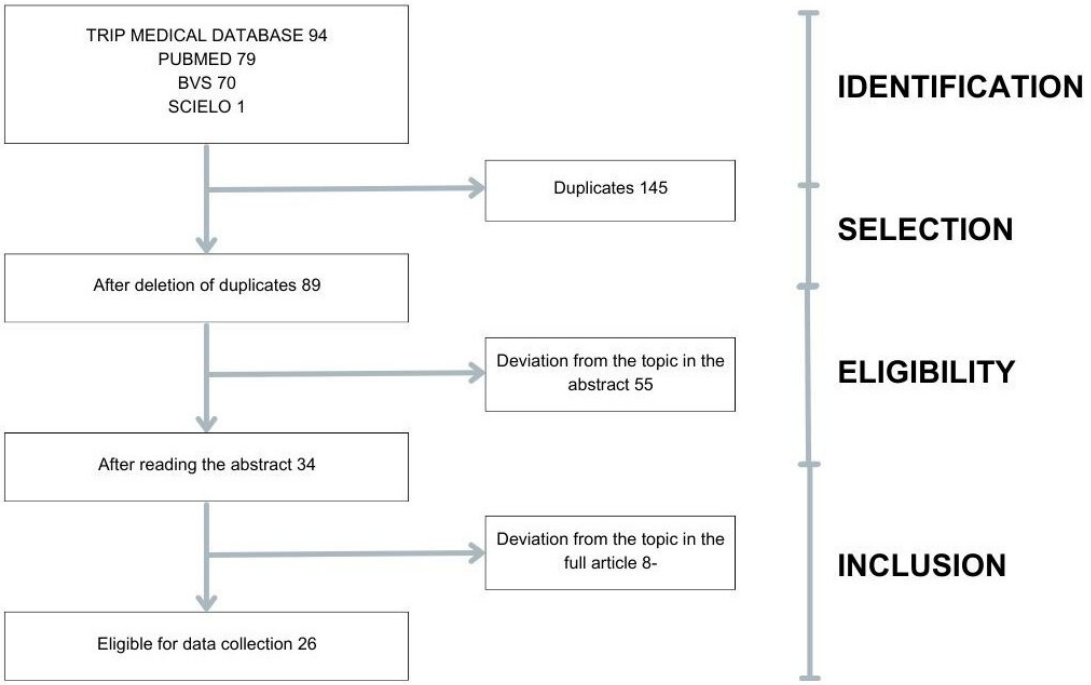

Figure 1 .PRISMA Flowchart for the application of inclusion and exclusion criteria for articles.

RESULTS AND DISCUSSION

A Common Variable Immunodeficiency (CVID) is the most prevalent clinically recognized form of primary immunodeficiency, characterised by hypogammaglobulinemia, leading to recurrent infections, particularly affecting the respiratory tract. However, non-infectious lung disease can also occur in association with this condition. Thus, patients with CVID and radiographic abnormalities may be predisposed to the development of interstitial lung diseases, a term that encompasses a heterogeneous group of acute and chronic lung conditions affecting the lung interstitium. Among interstitial lung diseases (ILDs), Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) is a common condition in CVID patients, with approximately 18% of patients developing this lung condition[10].

Computed tomography (CT) plays a crucial role in the investigation and management of interstitial lung diseases (ILDs), being of utmost importance in differential diagnosis, allowing detailed visualisation of the lungs, revealing changes in

density patterns, the presence of opacities, and lesion distribution. It also provides information for monitoring and tracking disease progression over time. According to the consensus observed by the British Lung Foundation in 2017[6], typical findings for GLILD diagnosis include the presence of solid or semi-solid nodules, ground glass opacity, splenomegaly, and hilar or mediastinal lymphadenopathy. Thus, from the analysis of the 26 eligible articles we aimed to list the main findings observing the consensus agreement with what is observed in practice, as well as evaluat the prevalence of bronchiolitis and ground glass opacity among the findings.

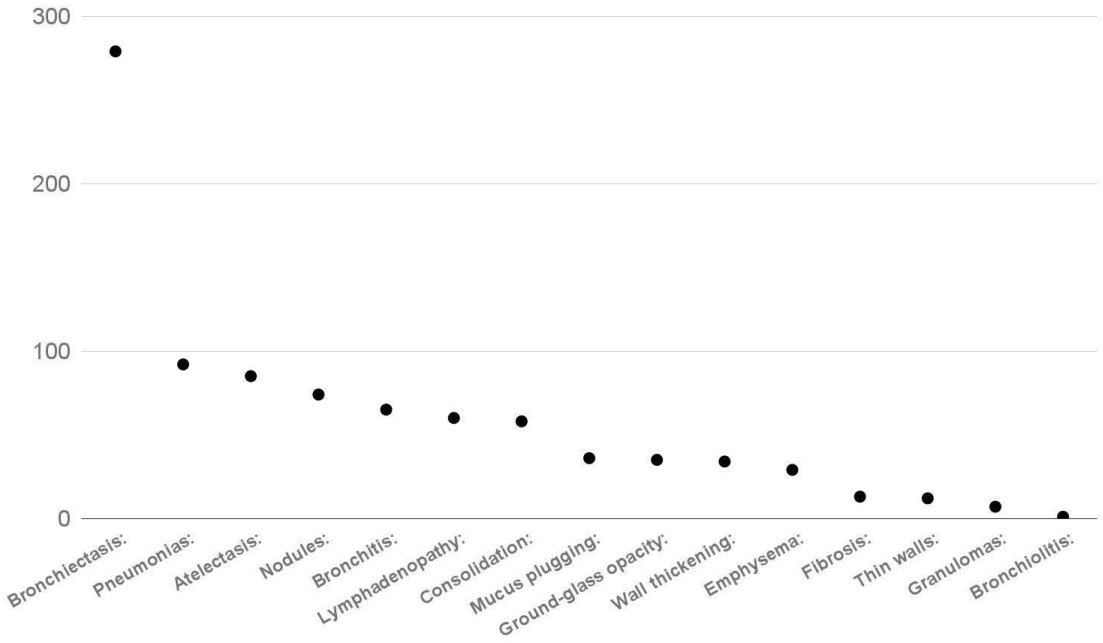

Figure 2. Main findings for the diagnosis of GLID in eligible articles

Among the 26 articles included in the review, the presence of a total of 775 CVID patients was observed. Of this number 564 had chest computed tomography with some abnormality. Among the radiological alterations, the following were identified: 279 patients with bronchiectasis, 92 with pneumonia, 85 with atelectasis, 74 with nodules, 65 with bronchitis, 60 with lymphadenopathy, 58 with consolidation, 36 with mucous plugging, 34 with ground glass opacities, 34 with wall thickening, 29 with emphysema, 13 with fibrosis, 12 with thin walls, seven with granulomas, and one with bronchiolitis (Figure 2).

Relating the findings to the diagnostic criteria suggested in the British Thoracic Society consensus for GLILD, it is observed that 9.55% of the total number of CVID patients had solid or semi-solid nodules, 7.74% had lymphadenopathy, and 4.39% had ground glass opacities. Splenomegaly was mentioned in 3 articles: one case series where all three patients had GLILD and only one did not have splenomegaly[11], and two case reports where individuals had GLILD and splenomegaly[12]. As an unusual finding it was observed that bronchiectasis, which is not a typical feature of GLILD, was the most common modification observed in the articles. However, given the correlation of this finding with respiratory tract infections and the study's limitation in describing infections in the patients observed, one can assume the correlation of this finding with recurrent infections in CVID. Thus, the study was limited by the lack of follow-up and individualised information for each patient.

Regarding countries, seven studies were conducted in England, six in the United States, four in the Netherlands, two in Iran, one in Italy, Spain, Singapore, Argentina and Japan, one was not mentioned, and one involved more than one country. Most of the publications found were from the last four years.

CONCLUSION

Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) is one of the possible conditions caused by Common Variable Immunodeficiency (CVID), affecting up to one in five patients diagnosed with CVID. This study aimed to assess the pattern of tomographic findings in CVID patients, with an emphasis on bronchiolitis and ground glass opacity, for the diagnosis of GLILD.

The results showed that the percentage of patients presenting such comorbidities in chest Computed Tomography scans was insignificant, with no significant epidemiological evidence in the reviewed literature suggesting the importance of incorporating ground glass opacity and bronchiolitis findings in the classification of CVID cases. Likewise, the findings proved to be extremely diverse, making it impossible to establish a pattern of observed tomographic findings.

Furthermore, a high incidence of bronchiectasis was observed, which according to the British Lung Foundation does not constitute one of the classificatory diagnostic

criteria for GLILD. Regarding splenomegaly as a necessary finding for GLILD diagnosis, there is a scarcity of reports identifying the presence of this comorbidity in patients with the disease, as splenomegaly was described in only four out of 207 patients with a confirmed diagnosis of GLILD. Therefore, further studies are needed to quantitatively correlate the percentage of patients with splenomegaly who also have pulmonary comorbidity, highlighting its importance as a diagnostic criterion.

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