Interstitial lung disease in primary immunodeficiency: towards a brighter future

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The ERS eGLILDnet CRC is working for better care and research for people affected by GLILD http://bit.ly/37WZGdd

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Lung disease is a frequent clinical manifestation in people living with primary immunodeficiency diseases, the most prevalent of which are common variable immunodeficiency disorders (CVID). CVID is primarily characterised by antibody deficiency, but recent definitions and diagnostic criteria recognise a much more complex pattern of immunological defects [1]. CVID can be classified into two major clinical phenotypes. One group experiences infection as the only major clinical manifestation, whilst the other present a variety of lymphoproliferative, inflammatory and/or autoimmune complications. The most frequent consequences in the lung of CVID are acute infections, and secondary airway complications of infection, such as bronchiectasis. However, up to 15% of patients with CVID develop an interstitial lung disease [2, 3]. Infections and bronchiectasis are primarily driven by antibody deficiency, but CVID associated interstitial lung disease (CVID-ILD) is best considered part of a systemic immune dysregulatory process [4] such that people with CVID-ILD often have splenomegaly, lymphadenopathy and autoimmune cytopenias [5–7]. With an EU population of 747 million, we estimate there are up to 30 000 people living with CVID in Europe, and thus 4500 with CVID-ILD. Whilst people with "infection only" CVID can now expect a near normal life expectancy [8], those with systemic immune dysregulation including CVID-ILD often have a much more complicated course. CVID-ILD increases morbidity and mortality in CVID [9], although the outcome is now recognised to be more variable than originally reported [10].

The terminology in use for ILD in CVID is complex and there is no consensus. The term granulomatous-lymphocytic interstitial lung disease (GLILD) is in common use but there need not be granuloma. We previously proposed the following working definition of GLILD: "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" [11]. Lung pathology and its radiological correlate in CVID-ILD/GLILD are heterogeneous including frequent ground-glass opacities due to lymphocytic interstitial pneumonitis, organising

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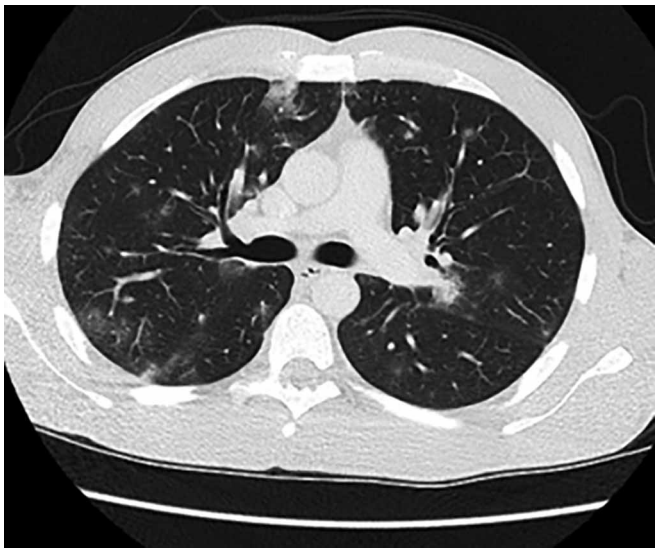

FIGURE 1 Typical computed tomography (CT) chest scan from a patient with common variable immunodeficiency disorder at the time of initial diagnosis with granulomatous-lymphocytic interstitial lung disease. The patient was asymptomatic but had impairment in gas transfer. The CT also demonstrated splenomegaly.

pneumonia, and larger, often bronchocentric nodules, often in the context of background bronchiectasis (figure 1) [12, 13]. No pathogen has been identified and the mechanism is likely immune dysregulation. Histology is characterised by combined T- and B-lymphocytic infiltrates, partly creating tertiary lymphoid structures within the lung and associated with increased levels of the B-cell activating factor BAFF [14]. The frequent coincidence of lymphadenopathy raises the important differential diagnoses of sarcoid and lymphoma. Associated laboratory abnormalities include elevated soluble interleukin-2 receptor, β2 microglobulin and neopterin, together with the hypogammaglobulinaemia that is the hallmark of CVID and which facilitates differentiation from sarcoidosis in previously undiagnosed patient with CVID-ILD.

Managing patients with rare diseases is challenging in the absence of robust evidence. Many questions about the pathogenesis, diagnosis and management of GLILD remain. Is a lung biopsy necessary? What constitutes optimal treatment given that the available evidence, such as it is, remains based on case reports and small case series [15–18]? The relevance of B-cells in the pathogenesis of CVID-ILD/GLILD is underlined by the reported effectiveness of rituximab [19]. New treatments in ILD such as nintedanib and pirfenidone have not been tested in CVID-ILD/GLILD, although fibrosis is not a prominent feature of CVID-ILD/GLILD.

To understand current management, we conducted a survey in the UK to assess diagnostic work up, and how clinicians were making treatment decisions including starting criteria, choice of drug, and endpoints such as symptoms, lung function and radiology [11]. The large (observational) European STILPAD (Study of interstitial lung disease in primary antibody deficiency) study will shortly report retrospective results, adding to the existing literature. Such evidence is urgently required to better treat people with this condition.

With considerable progress in understanding and treating other ILD, it becomes increasingly frustrating and unacceptable not to address the challenges in managing CVID-ILD/GLILD. To this end, we are pleased to announce the launch of a European Respiratory Society Clinical Research Collaboration (ERS CRC) to address CVID-ILD/GLILD, called eGLILDnet. As has been previously described, ERS CRCs are established to promote the exchange of research ideas among clinicians and scientists in Europe and more widely and to plan, conduct, evaluate and publish clinical and translational studies [20].

eGLILDnet will create a multi-professional network that is designed to establish a virtual multidisciplinary team for case-based expert discussion in collaboration with ERN RITA, and a registry for cases (ERN RITA is the European Reference Network for immunodeficiency, autoinflammatory and autoimmune disease). We will go on to complete a research prioritisation exercise, ultimately advocating for and delivering necessary practice changing research in CVID-ILD/GLILD. Only by wide, transparent, multi-professional and trans-disciplinary collaboration across Europe can we strive to deliver a brighter future for those affected by CVID-ILD/GLILD. Like all CRCs, eGLILDnet is a collaboration of patients, clinicians, scientists and industry, and designed to support training through the involvement of early career researchers.

How can you help? If you would like to join us, please contact the co-chairs. You can follow updates on Twitter (@glildnet) or at our website (www.ersnet.org/research/e-glildnet—a-european-granulomatous-lymphocytic-interstitial-lung-disease-network).

And practically? Always remember to measure serum immunoglobulins in people with SPUR (severe, persistent, unusual or recurrent) infections, bronchiectasis and interstitial lung disease, particularly sarcoidosis, to avoid missing primary immunodeficiency.

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