The broad spectrum of lung diseases in primary antibody deficiencies

Francesco Cinetto[1,2], Riccardo Scarpa[1,2], Marcello Rattazzi[1,2] and Carlo Agostini[1,2]

Affiliations: [1]Dept of Medicine – DIMED, University of Padova, Padova, Italy. [2]Medicina Interna I, Ca' Foncello Hospital, Treviso, Italy.

Correspondence: Carlo Agostini, Dept of Medicine – DIMED, University of Padova, via Giustiniani 2, 35128 Padova, Italy. E-mail: carlo.agostini@unipd.it

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The spectrum of lung complications in primary antibody deficiency ranges from asthma or COPD to extremely rare and specific ILDs. Early diagnosis of the underlying immune defect might significantly improve patients' lung disease, QoL and long-term prognosis. http://ow.ly/5cP230kZvOB

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ABSTRACT Human primary immunodeficiency diseases (PIDs) represent a heterogeneous group of more than 350 disorders. They are rare diseases, but their global incidence is more relevant than generally thought. The underlying defect may involve different branches of the innate and/or adaptive immune response. Thus, the clinical picture may range from severe phenotypes characterised by a broad spectrum of infections to milder infectious phenotypes due to more selective (and frequent) immune defects. Moreover, infections may not be the main clinical features in some PIDs that might present with autoimmunity, auto-inflammation and/or cancer. Primary antibody deficiencies (PADs) represent a small percentage of the known PIDs but they are the most frequently diagnosed, particularly in adulthood. Common variable immunodeficiency (CVID) is the most prevalent symptomatic PAD.

PAD patients share a significant susceptibility to respiratory diseases that represent a relevant cause of morbidity and mortality. Pulmonary complications include acute and chronic infection-related diseases, such as pneumonia and bronchiectasis. They also include immune-mediated interstitial lung diseases, such as granulomatous-lymphocytic interstitial lung disease (GLILD) and cancer. Herein we will discuss the main pulmonary manifestations of PADs, the associated functional and imaging findings, and the relevant role of pulmonologists and chest radiologists in diagnosis and surveillance.

Introduction

Human primary immunodeficiency diseases (PIDs) represent a heterogeneous group including more than 350 distinct disorders, mainly defined by specific underlying gene defects [1, 2]. They are classified within the "rare diseases", but their global incidence has been suggested to be more relevant than generally thought [3]. A recent study estimated that worldwide 6 million people might be living with a PID, of which only 27 000–60 000 have been definitely diagnosed [4]. The International Union of Immunological Societies (IUIS) phenotypic classification groups PIDs into different categories according to the underlying immune defect. Defects may involve different branches of the innate and/or the adaptive immune response. Thus, diseases range from "broad spectrum" PIDs, affecting both cellular and humoral adaptive immunity (*e.g.* severe combined immunodeficiency), to extremely selective PIDs (*e.g.* specific antibody deficiency) [2]. Of note, the IUIS classification includes a number of diseases in which infections are not

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the major clinical features (*e.g.* auto-inflammatory disorders or hereditary angioedema), highlighting the strong relationship existing between immunodeficiency, autoimmunity and autoinflammation. An increased incidence of cancer has also been described in PID patients [5, 6].

Most of the disorders included in the IUIS classification are extremely rare and clinical presentation occurs in the first days of life or during early childhood. Long-term prognosis may be poor. Although representing a small percentage of the IUIS listed diseases, primary antibody deficiencies (PADs) are less rare, have a better long-term prognosis and are often diagnosed in adulthood, thus accounting for the majority of diagnosed PIDs. The impairment in antibody production may be related to B-cell intrinsic or B-cell extrinsic defects, with the precise aetiology being mainly unknown. The most prevalent symptomatic PAD, common variable immunodeficiency (CVID), is indeed one of those PIDs whose genetic basis is still poorly understood [7].

Amongst PAD patients, respiratory disease is a relevant cause of morbidity and mortality [8]. As for other organ-related PAD manifestations, pulmonary complications include: infection-related, immune-mediated and neoplastic diseases. Respiratory tract infections (RTI) may be relevant when occurring acutely; their recurrence may also have long-term effects on the lung architecture, inducing airway remodelling (chronic obstructive pulmonary disease (COPD) and bronchiectasis). Immune-mediated complications include interstitial lung diseases (ILDs) and, in particular, a specific entity called GLILD (granulomatous-lymphocytic ILD). Finally, malignancies represent a major cause of morbidity and mortality in PAD and may involve the respiratory tract [5, 6, 8].

Herein we will discuss the main pulmonary manifestations of PADs and the associated functional, histological and radiological findings, highlighting the role of pulmonologists and chest radiologists in diagnosis and surveillance.

Primary antibody deficiencies

PADs include a spectrum of diseases ranging from X-linked agammaglobulinemia (XLA), where B-cell maturation is heavily impaired, to specific antibody deficiencies, where the disorder selectively involves the antibody response to polysaccaridic antigens. The impairment in antibody response is directed not only towards those microorganisms causing recurrent infections, but also towards vaccines designed to primarily elicit an antibody-mediated response, as 23-valent anti-pneumococcal vaccine. Poor response to vaccination is indeed one of the diagnostic criteria for CVID [9]. Apart from the infection-related features, PADs are generally characterised by an immune dysregulation that may lead to an increased incidence of allergy, autoimmunity, polyclonal lymphoproliferation, enteropathy and cancer [10–12].

Before discussing the acute and chronic lung complications, it is worthy to summarise the main features of the most relevant "predominantly antibody deficiencies".

Inheritance is usually X-linked (XLA, due to mutations on the BTK gene, occurring almost exclusively in males), but autosomal recessive or autosomal dominant forms have been reported [13]. It is characterised by the absence of mature circulating B-cells and by a severe decrease in all Ig subtypes. Due to the lack of B-cell co-stimulation, CD4+ T-cell differentiation may also be impaired [14]. Diagnosis often occurs within the first years of life. Sino-pulmonary infections, most often otitis, typically present after the sixth month of life in at least 60% of patients, as soon as the protection by maternal antibodies has waned. Severe bacterial infections (*e.g.* caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*) are common; pyoderma, conjunctivitis, septic arthritis, osteomyelitis and susceptibility to certain viral infections (*e.g.* enteroviruses) may also be increased [15, 16]. The development of chronic lung disease and progressive impairment of lung function has been shown to be related to the duration of follow-up, despite appropriate Ig replacement therapy [17, 18].

Hyper-IgM syndromes

This may be due either to a defect in T-cell dependent B-cells co-stimulation (*e.g.* defective CD40:CD40 ligand interaction), or to an impairment in the class switch recombination process (*e.g.* mutations in AID or UNG genes). As a consequence, patients present with a severe reduction in serum IgG and IgA, with normal or elevated IgM and normal numbers of circulating B-cells. They are prone to sino-pulmonary and gastrointestinal infections, as well as autoimmune diseases [16]. When the mutation specifically affects class switch recombination, the clinical phenotype may be that of a pure humoral immunodeficiency. The impairment of the CD40:CD40 ligand interaction may also affects cellular immunity, leading to increased susceptibility to opportunistic infections like *Pneumocystis Jirovecii* [19, 20].

Selective IgA deficiency

This is defined by very low or absent circulating IgA ($< 7 mg \cdot dL^{-1}$) with normal IgG and IgM in individuals aged $\geqslant 4$ years. IgG subclasses and specific antibodies are normal, as well as circulating B-cells.

Selective IgA deficiency is the most common primary immune defect with a prevalence of about one in 600 individuals in Europe and North America [21]. Approximately two-thirds of diagnosed patients are asymptomatic, while the remaining one-third may suffer from bacterial infections, gastrointestinal disorders, autoimmunity and atopy [22]. A moderately increased risk of cancer has been reported, particularly affecting the gastrointestinal tract [11, 23].

IgG subclass deficiency

This is characterised by a reduction in one or more IgG subclasses, generally IgG1, IgG2 and/or IgG3. When not associated with IgA deficiency, it is usually asymptomatic but a minority of patients may have poor antibody response to specific antigens and recurrent viral/bacterial infections [24, 25]. Impaired polysaccharide vaccine responses can be a specific feature of IgG2 subclass deficiency, thus explaining an increased incidence of infections by encapsulated bacteria [16].

IgG subclass deficiency with IgA deficiency

IgA deficiency may be associated with IgG subclass deficiency, particularly the IgG2 subclass. This results in a more relevant infectious phenotype, if compared to the previously described two separated entities [21]. Recurrent sino-pulmonary infections may be the most common clinical features, potentially leading to chronic infections and bronchiectasis.

Specific antibody deficiency

This is diagnosed by demonstrating a poor response to a pure polysaccharide vaccine (the 23-valent pneumococcal polysaccharide vaccine is the gold standard) in patients at least 2 years of age with normal B-cells, IgG and IgG subclasses [26]. The genetic basis in unknown; the reduced ability to produce antibodies to specific antigens, namely polysaccaridic as for *S. Pneumoniae*, may lead to severe and recurrent sino-pulmonary infections driven by the same pathogen, despite history of specific vaccination. Without appropriate management, including additional vaccinations, antibiotics and Ig replacement, permanent sequelae may occur (*e.g.* bronchiectasis) [26]. Specific antibody deficiency may be associated with IgA deficiency [16].

Common variable immunodeficiency

CVID is defined by low IgG and IgA and/or IgM serum levels in patients aged >4 years showing poor response to vaccination and/or low switched-memory B-cells. Any possible cause of secondary hypogammaglobulinemia must be ruled out [9]. CVID includes a heterogeneous group of antibody disorders, with an estimated incidence between 1:25 000 and 1:50 000 and equal sex distribution. Despite the high degree of under diagnosis, CVID is the most commonly diagnosed symptomatic PID.

Recurrent bacterial infections (mainly sino-pulmonary) represent the main feature, often associated with autoimmunity (*e.g.* immune cytopenias), gastrointestinal involvement, splenomegaly, lymphoproliferative disorders and granulomatous infiltration of various organs. End-stage organ damage and malignancies are major causes of death [6]. Despite being mainly a B-cell related disorder, T-cell abnormalities can occur, possibly related either to a defect in the cross-talk between T- and B-cells or to an impairment in T-cell signalling [27, 28].

The onset of symptoms can occur at any age, with a first peak during childhood and a second peak in the third and fourth decades of life. The frequent onset in adulthood, the heterogeneity of non-infectious manifestations and the variability of the infectious phenotype (from severe to mild or almost absent) give reason for a significant delay between initial symptoms and formal diagnosis. Diagnostic delay has been reported to be >5 years, on average, in developed countries. This, in turn, implies a postponement in receiving appropriate treatment, with a consequent impact on quality of life, morbidity and mortality [29, 30].

Other primary antibody deficiencies

Over the past few years, specific PADs previously classified as CVID have been identified as being related to specific gene mutations; some of these diseases might predispose to specific lung manifestations. In this context, it is worthy to mention activated PI3K-δ syndrome and cytotoxic T-lymphocyte associated protein-4 deficiency [31, 32].

In activated PI3K-δ syndrome, a monogenic autosomal dominant gain of function mutation leads to uncontrolled lymphoproliferation. Patients present with reduced serum IgG2, poor response to vaccination and recurrent respiratory infection with airway damage. The expansion of lymphoid tissue in the lung may lead to bronchial compression, with characteristic radiological and bronchoscopic appearances and possible post-stenotic pneumonia [33].

Cytotoxic T-lymphocyte associated protein-4 deficiency is an autosomal dominant syndrome characterised by immune dysregulation with activation of T-cell compartment. The impairment in regulatory T-cell function may open the way for auto-reactive immune infiltration of the lungs, often leading to GLILD [34].

Finally, autosomal dominant signal transducer and activator of transcription 3 (STAT3) gain of function mutations have been described. These mutations lead to early-onset and severe multi-organ autoimmunity (cytopenias, enteropathies and/or lymphocytic ILDs), associated with hypogammaglobulinemia and lymphoproliferative complications. The clinical phenotype is highly variable. Immune dysregulation may lead to recurrent and severe infections by a broad spectrum of pathogens, including opportunistic infections [35].

Pulmonary complications of PADs

The respiratory tract is the major target for infections and their sequelae in PADs, and pulmonary complications affect ∼60% of patients with PAD and up to 90% of those affected by CVID. [36]. This implies a high rate of referral to pulmonologists, who may be the first specialist encountered by these patients. PADs have indeed been suggested as a relevant unrecognised cause of chronic respiratory disease [37]. Moreover, even after a diagnosis of PAD, pulmonologist are usually the first specialist to whom patients are referred. An early detection of the underlying immune defect and the consequent establishment of appropriate treatment strategies may significantly reduce the occurrence of new infections and of long-term lung damage [29, 38, 39]. On the contrary, diagnostic delay may be responsible for some degree of permanent impairment in lung function in up to 54% of patients [38, 40].

Infection-related and immune-mediated lung diseases

Different and still poorly understood cofactors may lead PADs patients' lung, when affected, towards a more infectious-related degenerative pattern (*e.g.* bronchiectasis and early COPD) or an immune-mediated ILD (*e.g,* GLILD) [28, 41]. All things considered, clinicians are not simply facing two sides of the same coin, but more appropriately a Janus Bifrons disease, possibly combining immune deficiency and immune-mediated disease [42].

Infection-related lung disease

Infection-related pulmonary manifestations, either acute (pneumonia) or chronic (bronchiectasis and COPD), have already been extensively discussed [43–45]. The role of the immune defect is well defined, particularly in bacterial infections and their recurrence. The defect also impacts on the increased time for complete healing despite appropriate treatment, the high rate of colonisation in cases of bronchiectasis and a consequent high degree of antibiotic resistance, due to the widespread use of antibiotic treatment and prophylaxis [45].

Acute infections

Before and despite adequate Ig replacement, recurrent RTIs are the commonest clinical feature in symptomatic PADs and have great impact on patients' quality of life [43, 46, 47]. Upper and lower RTIs are included in the list of 10 warning signs for PID promoted by the Jeffrey Model Foundation [48, 49].

Pneumonia due to bacterial agents is the most frequently identified acute infection in PID patients before a diagnosis of CVID or XLA is established. It has been reported that >50% of patients presenting with pneumonia require hospitalisation [29, 50, 51].

Therapeutic approach

PAD patients are often prescribed oral antibiotic treatment both to promptly self-administer during symptom onset and as prophylaxis to reduce infection frequency. Thus, the use of antibiotics in PAD cohorts is many times higher than in the general population. However, a recent prospective cohort study showed a relevant delay in commencing antibiotic therapy for breakthrough infections in CVID patients on regular antibiotic prophylaxis [45]. In the case of a lower RTI with purulent sputum, empiric broad-spectrum antibiotic treatment is generally initiated. When sputum or bronchoalveolar lavage samples are cultured, a specific treatment is established on the basis of the antibiogram [41]. The frequent finding of encapsulated bacteria highlights the relevance of antibody-mediated opsonisation for their immune clearance (table 1) [28, 46].

The impact of IgG replacement therapy on the infectious phenotype has been highlighted previously [29, 44]. In a cohort of CVID and XLA patients, a significant reduction in the prevalence of pneumonia and a drastic reduction in the incidence of invasive infection were observed after initiation of Ig replacement therapy. A significant increase in risk for pneumonia has been found with a serum IgG

TABLE 1 Isolated pathogens in respiratory tract infections in patients with primary antibody deficiencies

Type of agent	Isolated agents	Reference
Most frequently reported bacteria	*Streptococcus pneumoniae, Haemophilus influenzae* type B, *Neisseria meningitidis, Moraxella* spp., *Staphylococcus* spp. (including methicillin resistant), *Streptococcus* spp., *Pseudomonas aeruginosa, Mycoplasma* spp.	[41, 45, 49, 52–56]
Other reported bacteria	*Klebsiella* spp., *Bordetella pertussis, Chlamydia trachomatis, Ureaplasma urealyticum, Fusobacterium* spp., *Serratia* spp., *Stenotrophomonas maltophilia*, *Enterobacter* spp., *Proteus* spp., *Achromobacter xylosoxidans, Citrobacter* spp.	[41, 45, 49, 52–56]
Virus	Rhinovirus, adenovirus, coronavirus, influenza A and B, enterovirus, RSV, hMPV	[41, 57, 58]
Opportunistic pathogens (rare, reported in XLA and HIGM)	*Mycobacterium hominis, Mycobacterium avium, Pneumocystis jirovecii*	[19, 41, 53, 56, 59, 60]

XLA: X-linked agammaglobulinemia; HIGM: hyper-IgM syndrome; RSV: respiratory syncytial virus; hMPV: human metapneumovirus. The most commonly isolated pathogens include *H. influenzae*, *S. pneumoniae*, *Pseudomonas* species, *Staphylococcus* spp. and *Mycoplasma* spp. [41].

trough level <400 mg·dL^{-1} in CVID patients and <500 mg·dL^{-1} in XLA patients. Lower IgA levels (<7 mg·dL^{-1}) resulted in an increased risk [29].

However, it has been reported that appropriate Ig replacement therapy does not prevent lung function decline in CVID (rate of decline is approximately twice the rate of healthy nonsmoking adults). Moreover, in some CVID patients and in XLA patients, chronic lung disease progression still occurs despite achieving adequate IgG trough levels [17, 44, 61]. In XLA, in particular, the only risk factor for developing chronic lung disease after diagnosis is the duration of follow-up (not IgG trough levels or age at diagnosis) [18, 62].

This may be due to a number of reasons but suggests that, in PADs, the impairment in immune defences might be broader than expected, involving multiple non-B-cell immunological defects, such as T-cell, mannose-binding lectin, Toll-like receptor and antimicrobial peptide deficiency, and/or impaired neutrophil function [41]. In line with this hypothesis, recent studies focused on the frequency of viral infections in PADs [45, 52]. In a study by Sperilch *et al.* [45], viruses accounted for 56% of isolated pathogens from nasopharyngeal swabs during symptomatic exacerbations in CVID patients, whilst bacteria were detected in 33% of sputum samples from the same patients. Bacterial and viral co-infection was detected in 25% of respiratory exacerbations. Co-infections were frequently observed in the presence of purulent sputum [45]. A list of the most involved pathogens is reported in table 1 [41, 45].

Of note, it has been suggested that infections of the small intestine due to parasites such as *Giardia lamblia* or, generally, an alteration of the gut microbiota might in turn enhance the susceptibility to respiratory infections by reducing the absorptive capacity of the gut both in terms of macro- and micro-nutrients. Moreover, viral (*e.g.* human herpesvirus-8) or protozoan pathogens (*e.g. Toxoplasma gondii*) have been implied in the pathogenesis of ILD [41, 63, 64].

Chronic lung disease: predominantly obstructive pattern

The most prevalent chronic infection-related pulmonary disease diagnosed in PAD patients is bronchiectasis. Other chronic respiratory complications include COPD and asthma, presenting an obstructive pattern during pulmonary function tests (PFTs), and chronic sinusitis [41, 65]. The recurrence of an acute RTI over an underlying chronic lung condition has prompted some researchers to classify these infections as respiratory exacerbation of CVID, mutating the definition from that already validated for COPD [45, 66].

Bronchiectasis

Bronchiectasis is a chronic disease affecting airways, presentation includes atypical bronchial and bronchiolar dilatation (figure 1a) [41, 67, 68]. This disorder is associated, in a "vicious cycle", with repeated episodes of infection and inflammation that result in destruction of the airways and lung parenchyma, leading to a decline in lung function (figure 1b) [41, 69]. In a recent retrospective study involving 801 adults with idiopathic hypogammaglobulinaemia and CVID, it has been reported that 59% of patients suffered from overt bacterial lower RTI and 47% from bronchiectasis [30]. History of lower RTI was the only factor directly associated with bronchiectasis [29, 30]. A similar "vicious cycle" may be the basis for chronic sinusitis in the same patients [29]. Immune defects not only involving the humoral compartment, as discussed above, are considered relevant factors in the development of bronchiectasis [41, 68].

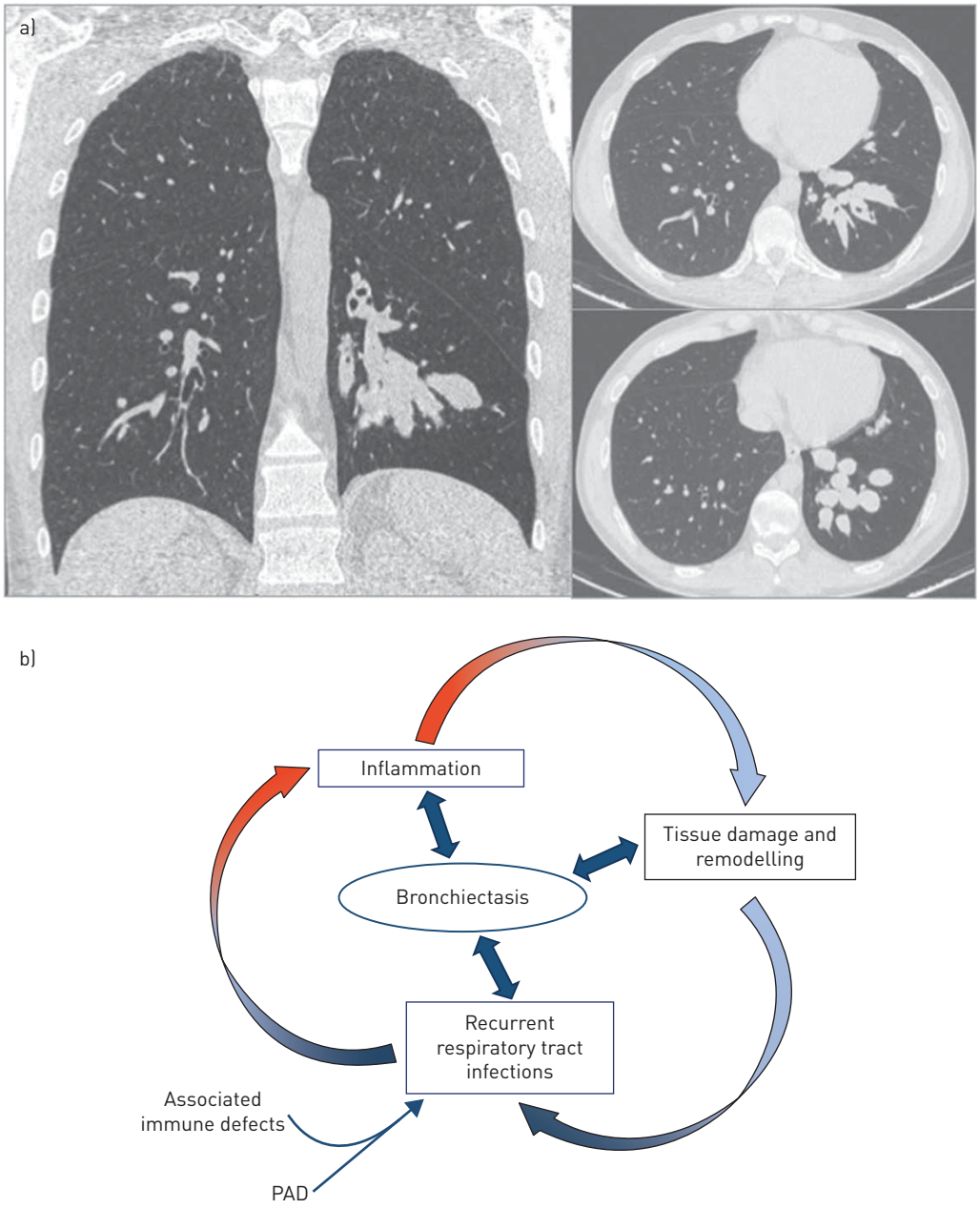

FIGURE 1 a) Mucus replete left lower lobe bronchiectasis in a young X-linked agammaglobulinaemia patient (coronal and axial view). b) Pathogenesis of bronchiectasis and chronic obstructive lung disease in primary antibody deficiencies (PAD). In patients with antibody deficiency, a vicious circle involving respiratory tract infections, inflammation and tissue damage/remodelling, possibly facilitated by concomitant non-antibody-related immune defects, might lead to bronchiectasis and fixed airway obstruction [41]. Recurrent infections may trigger recurrent asthma and chronic obstructive pulmonary disease exacerbations.

The management of bronchiectasis has been extensively studied in the context of cystic fibrosis (CF). Therapies for adult non-CF bronchiectasis, including those related to PIDs, are not as well standardised and tend to be simply extrapolated from CF clinical trials [70]. Despite lacking specific evidence, physiotherapy programmes and antibiotic prophylaxis are routinely used in PAD patients with bronchiectasis [71–73].

Physiotherapy is considered a standard adjunct to therapy in non-CF bronchiectasis, but there are currently no internationally recognised guidelines defining the best approach [62, 74]. Supervised pulmonary rehabilitation and exercise training programmes have shown short-term improvements in exercise capacity and health-related quality of life, but sustaining these benefits has revealed to be challenging [75]. The use of antibiotic prophylaxis with a macrolide and, in particular, azithromicyn, has

also been suggested in non-CF bronchiectasis for its interesting impact on respiratory exacerbations, quality of life and spirometry [76, 77]. Azithromycin, apart from its antibacterial power, is known to exert immunomodulatory effects in chronic lung disorders, including post-transplant bronchiolitis, CF and non-CF bronchiectasis, COPD and non-eosinophilic asthma [76]. A multicentre placebo-controlled trial on the use of prophylactic azithromycin in CVID patients has recently been completed in Italy, and results are expected to be available later this year. Waiting for these results, further studies are warranted to verify the optimal populations and clarify the potential effects of antibiotic prophylaxis on antimicrobial resistance and lung microbiota in PID patients [77].

Finally, the role of the microbiome and a series of emerging pathogens have also been highlighted in CF and non-CF bronchiectasis [78]. There is a lack of in-depth studies profiling the lung microbiota in PADs, but one could argue that the absence of mucosal IgA and the use of antibiotics may impact on the lung microbiota, as for the gut.

Asthma and COPD

Recurrent infections due to a primary immune defect may result in a chronic inflammatory response that leads to airway hyperreactivity and remodelling, and eventually to fixed obstruction (figure 1b). This has been hypothesised as a possible cause of COPD in those patients who never smoked and without a defect in α_1-proteinase inhibitor [37].

Asthmatic patients are more likely to receive a diagnosis of selective IgA deficiency/CVID than non-asthmatic individuals [79]. Thus, it has been suggested that this association might potentially account for the increased risk of bacterial infections in some individuals with asthma [79]. Another study showed bronchial hyperreactivity with methacholine challenge test in 42.5% of children affected by different PADs. Higher hyperreactivity correlated with a defect in IgA [80]. A correlation between IgG subclass deficiency and asthma has recently been highlighted [81].

An increased prevalence of PAD has also been suggested in frequently exacerbating COPD patients, if compared to the general population. In a cohort of COPD patients complaining of two or more moderate-to-severe acute COPD exacerbations per year, despite being on maximal medical therapy for COPD, almost 70% were found to have an underlying PAD (CVID or specific antibody deficiency) [82].

Different studies confirmed the positive impact of Ig replacement therapy in improving asthma control status, ameliorating airway obstruction and reducing the frequency of exacerbations in asthmatic and COPD patients with previously undiagnosed PAD [83–85]. This means a reduction in courses of oral corticosteroids, cumulative annual dose of oral corticosteroids, rescue antibiotic use and hospitalisations for acute COPD exacerbations, and has implication both in terms of quality of life and healthcare costs. Of note, the recurrent or long-term use of systemic steroidal treatment in COPD and asthmatic patients may in turn affect the γ-globulin serum levels, thus complicating the distinction between primary and secondary antibody deficiency [86]. Nonetheless, all these reports suggest the need for a higher index of suspicion in clinical practice, in order to avoid under diagnosis of PADs in severe uncontrolled asthmatic and frequently exacerbating COPD patients. Further studies are warranted to clarify the actual relevance of PADs in asthma and COPD [37].

Immune-mediated lung disease

Nowadays, the greatest challenge is represented by the PAD-related ILDs, where immune dysregulation definitely plays a major role but whose pathogenic mechanisms are still far from being understood.

Chronic lung diseases: predominantly restrictive pattern

PAD-related ILDs represent a group of chronic inflammatory diseases whose onset is often insidious. They tend to become symptomatic in later stages, when pulmonary fibrosis may be complicated by pulmonary hypertension, cor pulmonale and progressive respiratory failure. PFTs may show a restrictive pattern. A decrease in diffusion capacity of the lung for carbon monoxide could be an early sign of ILD that should be monitored by additional functional testing, such as 6-min walk test or imaging (high-resolution computed tomography; HRCT) [87]. It has been suggested that ILDs rather than recurrent infections and related bronchiectasis might be the main cause of a decline in lung function in patients with CVID [8].

In PAD patients with recurrent respiratory infection, ILDs are more frequent and much more prevalent than expected in the general population [8, 53, 88]. It has been reported that ILD occurs in at least 10–20% of CVID patients, but the actual prevalence might be higher [89, 90]. It is also occasionally seen in IgA deficiency, particularly when associated with IgG subclass deficiency and relevant autoimmune phenotype, with similar functional and radiological features [16]. ILD appears to be a relatively common feature of cytotoxic T-lymphocyte associated protein-4 haploinsufficiency and STAT3 gain of function

mutations [34, 35]. Hypomorphic mutations in recombination-activating gene 1 (*RAG1*), and deficiency in lipopolysaccharide responsive beige-like anchor protein (*LRBA*) have also been described in PAD patients with granulomatous or lymphocytic ILD [91–93]. However, there are no reports of ILDs in numerous studies on hyper-IgM syndrome and congenital agammaglobulinemia patients [16].

The broad spectrum of ILD in PAD, and particularly in CVID, includes follicular bronchiolitis, nodular lymphoid hyperplasia, granulomatous lung disease, lymphocytic interstitial pneumonia (LIP), non-specific interstitial pneumonia (NSIP) and organising pneumonia. Moreover, many types of PIDs carry an increased risk of systemic autoimmune disorders that may involve respiratory interstitial tissue (*e.g.* connective tissue diseases and vasculitis) [53]. Histological patterns may be overlapping and there is no consistent correlation between specific histological or radiological patterns and a particular immune deficiency [8].

Organising pneumonia, formerly known as bronchiolitis obliterans organising pneumonia, has been described as a frequent presentation in PADs [93–97]. It is a nonspecific reactive inflammation resulting from different causes of epithelial lung injury (infections, inflammation and fibrosis) and characterised by plugs of granulation tissue and spirals of fibroblasts, known as Masson bodies, in the alveolar spaces [16, 98]. The association of PAD with LIP and with a sarcoid-like disease has been known for many years [99–101].

The radiologic and histologic heterogeneity of ILDs in PAD has more recently led to the usage of the "umbrella" definition of GLILD. This term encompasses granulomatous disease and all forms of pulmonary lymphoid hyperplasia [90, 102]. However, GLILD is a term used exclusively in the context of PADs and whose exact borders may still not be clear. Indeed, non-neoplastic lymphoproliferative diseases such as LIP can intrinsically present both granulomatous and organising pneumonia histological features [16].

GLILD

A recent British Lung Foundation/United Kingdom Primary Immunodeficiency Network consensus statement defined GLILD as "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" [103]. It was also stated that GLILD is usually seen in the context of multisystem granulomatous/inflammatory disease, which might include symptomatic or asymptomatic involvement of the spleen, lymph nodes, liver, gastro-intestinal tract and/or other organs [103, 104]. Despite the different ILD patterns having been described in PADs, GLILD is reported as the most common and closely associated with poor clinical outcomes. Thus, it is currently the main focus of investigation in this field [8, 28, 101].

Sarcoid-like non-caseating granulomas, peri-bronchiolar and interstitial lymphocytic infiltration (resembling the pattern of LIP and follicular bronchiolitis) are the main histopathological features. Extensive organising pneumonia and pulmonary interstitial fibrosis are also seen in a significant proportion of patients (figures 2c and S2). Apart from follicular bronchiolitis and LIP, other forms of pulmonary lymphoid hyperplasia may be present as nodular lymphoid hyperplasia and reactive lymphoid infiltrates. Of note, in these contexts, the ectopic B-cell follicles express markers of germinal centres and proliferation despite the underlying B-cell maturation defects [90]. In most patients, T-cells (particularly CD4+) are the predominant lymphocyte population in the lung, with B-cells present to a lesser extent. A minority of cases display B-cell tissue predominance. A near total absence of regulatory T-cells has also been reported [93, 101].

The differential diagnosis of GLILD includes infections, other defined ILDs (sarcoidosis, chronic hypersensitivity pneumonitis, NSIP and usual interstitial pneumonia), and malignant lymphoproliferative diseases. Thus, definitive diagnosis relies on a high index of suspicion, a clinical and microbiological correlation and a histopathologic confirmation in individuals with PAD [93]. The frequency and prominence of an organising pneumonia histological pattern within the heterogeneous pathologic picture gives reason for suggesting an open lung or video-assisted thoracoscopic surgery biopsy whenever it can be safely performed, in order to provide the pathologist with an adequate sample.

Sarcoidosis shares the histological recognition of non-necrotising granulomas with possible multi-systemic involvement with GLILD [16, 105, 106]. The main features distinguishing GLILD from sarcoidosis are summarised in table 2.

As for sarcoidosis, GLILD pathogenesis is far from being understood, but it has been hypothesised as a role of recurrent or unrecognised infections (*e.g.* human herpesvirus-8) [39, 107–109]. At the same time, the absence of GLILD reports in hyper-IgM syndrome and XLA patients suggests that possible infectious triggers might require the co-existence of discrete immune defects or discrete patterns of immune

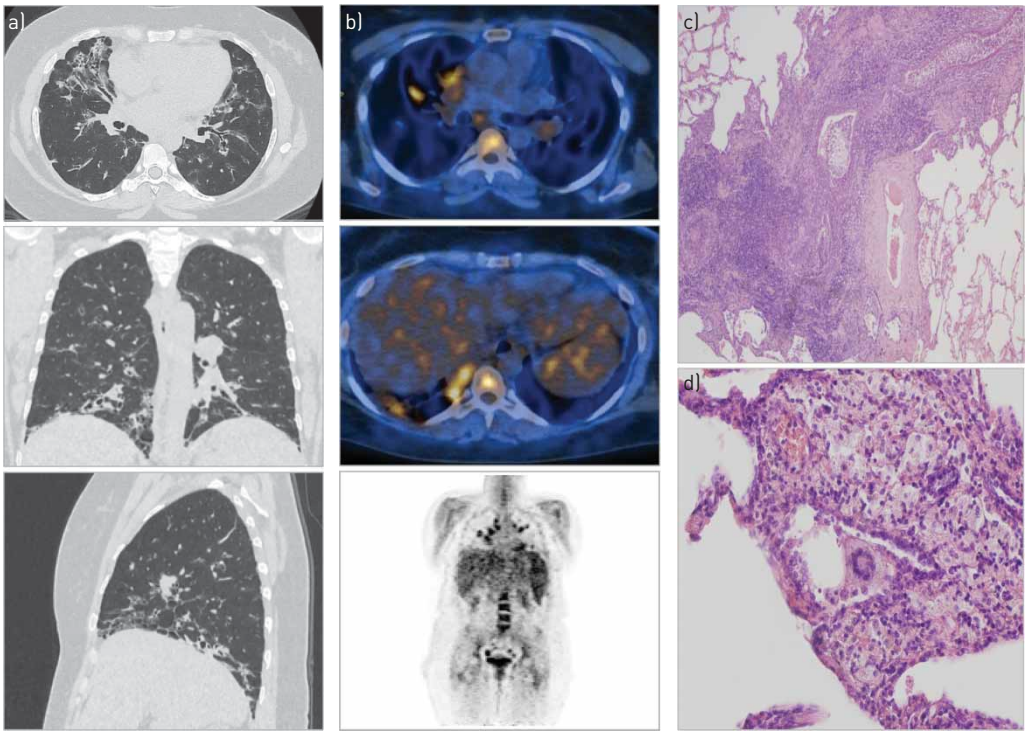

FIGURE 2 Radiological and pathological findings in a common variable immunodeficiency patient with granulomatous-lymphocytic interstitial lung disease. a) High-resolution computed tomography: axial, coronal and sagittal views show several nodules with peri-lymphatic distribution without predominance in the upper lobes, and the co-existence of bronchiectasis. b) Positron emission tomography/computed tomography findings shows hilar lymph nodes and peri-lymphatic nodules on fluorodeoxyglycose (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. c, d) Pathological findings from surgical lung biopsy. c) Bronchiolar and peri-bronchiolar inflammation with follicular bronchiolitis and contiguous parenchymal involvement (haematoxylin and eosin staining, ×25 original magnification). d) Microgranuloma with a giant cell surrounded by foamy and epithelioid macrophages (haematoxylin and eosin staining, ×200 original magnification).

dysregulations in order to promote this specific ILD or systemic disease. An increased number of circulating $CD8^+$ T-cells (which supports an aetiologic role for intracellular infections) has been described in paediatric CVID patients with GLILD [110]. An association between GLILD and circulating B-cells has also been suggested, namely with low numbers of marginal zone and switched memory B-cells and with an increase in activated CD21low B -cells [89, 111, 112].

Bronchoalveolar lavage fluid (BALF) cytology in adult CVID patients with a diagnosis of GLILD has been described as lymphocyte enriched (>20%). Both an increased and a normal CD4/CD8 ratio of BALF lymphocytes have been reported [105, 113, 114]. CD21low B-cells have also been claimed as the dominant cells in the BALF of patients diagnosed with GLILD [96]. These findings may suggest possibly distinct pathogenic mechanisms of GLILD in different patients, which might derive from diverse triggers and be correlated to heterogeneous clinical and prognostic phenotypes [113, 114]. Further work is needed, however, to elucidate the contribution of these lymphocyte sub-populations to the development of ILD and to understand whether flow–cytometric analysis of BALF cells may have any diagnostic or prognostic value, in the absence of histological examination, as it is for sarcoidosis [28, 115]. Thus, bronchoalveolar lavage is currently indicated only to exclude infections. The role of trans-bronchial biopsy is not defined [102]. Cryobiopsy might be a more interesting approach [116].

Considering the clinical and histopathological heterogeneity and the relatively late onset of functional impairment and symptoms, recent retrospective studies have investigated on clinical or serological indexes able to identify a subset of PAD patients with higher risk for developing GLILD. Splenomegaly, history of immune cytopenias (idiopathic thrombocytopenic purpura or autoimmune haemolytic anaemia), low

TABLE 2 Main features of granulomatous-lymphocytic interstitial lung disease (GLILD) and sarcoidosis

Main features	GLILD	Sarcoidosis
Gamma globulin	Generally decreased (may be normal in IgG subclass deficiency), low serum IgA level and higher IgM levels have been reported	Normal or increased, no specific Ig class or subclass level alteration
ACE	Generally normal	Often increased
Decreased circulating switched-memory B-cells	Frequent	Not reported
Increased circulating CD21 low B-cells	Frequent	Not found
BALF lymphocytosis	Frequent (>20%)	Frequent
Elevated BALF CD4:CD8 ratio	Reported in a small case series	Typical in acute Lofgren Syndrome
Recurrent infections	Generally reported	Infrequent
Autoimmune cytopenia	Frequent	Not associated, cytopenia may be due to bone marrow granulomatous infiltration or splenomegaly
Splenomegaly	Frequent	Spleen may be involved, splenomegaly is infrequent and generally secondary to severe liver disease
Nodular regenerative hyperplasia of the liver	Increased likelihood	Liver involvement is often asymptomatic, biopsies may show granulomatous hepatitis
Gastrointestinal involvement	Reported in 15%	Rare
Eye involvement	Not reported	Frequent
PLH histological and radiological evidence (*e.g.* LIP and FB)	Typical	Not present
Hilar adenopathy	May be present	Typical feature
Lung nodules size and distribution on HRCT	Often >1 cm, with random or predominantly basal distribution	Typically <1 cm, with mainly apical and peri-lymphatic distribution
Bronchiectasis	Frequent	Traction bronchiectasis may be found in advanced fibrotic disease
Prognosis	Slowly progressing restrictive lung disease with poor prognosis	Generally good prognosis, spontaneous remission may frequently occur, particularly in acute (Lofgren Syndrome) presentation

ACE: angiotensin converting enzyme; BALF: bronchoalveolar lavage fluid; PLH: pulmonary lymphoid hyperplasia; LIP: lymphocytic interstitial pneumonia; FB: follicular bronchiolitis; HRCT: high-resolution computed tomography; Ig: immunoglobulin. Data from [16, 105, 106].

serum IgA levels, higher IgM levels and percentage expansion of CD21low B-cells have been suggested as highly sensitive predictors of GLILD [117, 118].

HRCT is the gold standard imaging technique for ILDs and, in specific cases and in the context a multi-disciplinary team evaluation, can lead to a diagnosis without need for histologic confirmation [119]. In GLILD patients it may show bronchiectasis, bronchial wall thickening, air trapping, parenchymal consolidation, emphysema, reticular and/or nodular changes and/or fibrosis, with or without ground-glass opacities, predominantly affecting the lower lobes (figure 2a) [120, 121]. There are currently no validated radiologic scores for GLILD.

In a recent study, the use of fluorodeoxyglycose (FDG)-positron emission tomography/computed tomography (PET/CT) scanning has also been shown to be helpful in assessing and monitoring the response to treatment in CVID patients with GLILD [122]. Compared to HRCT, this technique has less morphologic power but can provide information on extrapulmonary involvement. Thus, it may be considered a complementary approach, particularly in the presence of systemic symptoms or when a lymphoproliferative disease has to be ruled out (figures 2b and S1).

Therapeutic approach

In line with the uncertainties about pathogenesis and diagnosis, specific treatment guidelines are lacking for GLILD. There are no data from controlled studies about treatment initiation or regarding the effectiveness of a specific therapeutic regimen. Only retrospective studies are currently available [96].

According to the above-mentioned consensus statement and to the limited available evidence, once a diagnosis of GLILD is made, the decision about whether to treat (or not) generally relies upon a combination of clinical and functional parameters. If the patient is asymptomatic and lung function is normal and not declining over time, specific treatment is not recommended. Optimisation of IgG

replacement therapy appears to be a valuable option, but no extensive data are available on the long-term effect of intravenous or subcutaneous Ig on GLILD [123, 124]. There is no evidence about the routine use of antimicrobial prophylaxis. Since an overlap of ILD with bronchiectasis is not rare, a concomitant antibiotic prophylaxis may be present in GLILD patients.

When patients are symptomatic, present with an abnormal or a still normal but deteriorating lung function, it has been suggested to use corticosteroids as a first-line treatment [103, 125]. Extrapulmonary involvement may also influence the decision on treatment. A general consensus for azathioprine, rituximab and mycophenolate (in decreasing order of support) as second-line agents has been reported [101]. A recent retrospective study, in particular, reported successful treatment of GLILD with a combination regimen including rituximab and azathioprine [90]. There is currently no consensus on other reported treatments such as anti-tumour necrosis factor agents, hydroxychloroquine, methotrexate, mycophenolate, sirolimus or tacrolimus [103, 126].

The successful use of immune suppressants suggests that persistent infection may not contribute significantly to GLILD pathogenesis or progression, at least in some patients. This does not exclude infectious agents such as simple triggers, as hypothesised for other granulomatous diseases [96, 109].

Of note, azathioprine and rituximab have been shown to increase the number of regulatory T-cells, whose absence has been highlighted in GLILD lung samples. They are also known to be mainly effective on T- and B-cell mediated diseases, respectively [93, 127, 128]. Moreover, anti-CD20 treatment has been successfully used for T-cell-mediated and granulomatous diseases [129]. One could argue that, on the basis of tissue infiltration at histopathological analysis or according to BALF lymphocyte predominance, a more T-cell to B-cell targeted drug might be used as second-line treatment. However, we are still far from such a deep understanding of GLILD biology that may allow PAD specialists to design individualised treatment guidelines.

Neoplastic diseases involving the lung

Cancer is a major cause of death in PADs [6, 30]. Patients with CVID, in particular, are at increased risk of lymphoma and gastric carcinoma [130]. Different types of primary lymphoid lesions of the lung may be present in PID patients, including neoplastic lymphocytic proliferations as low-grade B-cell lymphoma of mucosa-associated lymphoid tissue, other non-Hodgkin lymphomas and Hodgkin lymphoma [131, 132]. These should be considered in the differential diagnosis of GLILD [133]. Lung carcinoma has also been reported in CVID, but infiltration of the lung with metastases (well-defined nodules of various sizes or ill-defined nodules with a peripheral halo) is more common than primary lung tumours [30, 53, 132].

Finally, the detection of a thymic enlargement/mass on a CT scan should raise the suspicion of thymoma-associated Good's syndrome rather than a CVID [134].

Screening protocols to monitor respiratory status and lung disease in PADs

There are no international consensus guidelines on how to screen PAD patients for lung disease [135]. Currently, a number of screening measures are used in different referral centres to diagnose and monitor lung complications. Apart from conventional radiologic imaging in cases of acute infections, different radiologic and functional tests may be useful at diagnosis and during follow-up of PADs.

Lung function (forced expiratory volume in 1 s and diffusing capacity of the lung for carbon monoxide in particular) have been shown to decline slowly over time in patients with PID. Thus, annual testing (both spirometry and transfer factor) is useful in the assessment of these patients, and should not be limited to those with radiological evidence of lung disease [73].

Apart from its use in acute lower RTI, HRCT currently represents the gold standard for diagnosing bronchiectasis and ILDs. In the diagnostic work-up of PADs, a HRCT scan of the chest should be obtained, if not performed recently, in order to assess any existing lung damage, that might strengthen the decision to initiate Ig therapy [136, 137]. It has been shown that only 6% of the patients have completely normal HRCT images [138].

HRCT is also used to monitor disease progression over time, although there are no internationally recognised guidelines suggesting how frequently this should be performed [62]. One of the concerns is represented by the balance between the risks of ionising radiation and the risks of missing a diagnosis of bronchiectasis or ILD. Thus, HRCT is generally performed on a clinical basis, but this increases the risk of a diagnostic delay in asymptomatic or pauci-symptomatic patients. PFTs may be helpful and diffusing capacity of the lungs for carbon monoxide reduction has been suggested as an early indicator of a possible underlying GLILD. The reliability of PFTs for early detection of lung disease has not been confirmed. A recent study in a CVID cohort showed that pre-clinical HRCT

TABLE 3 How we monitor and manage lung disease in primary antibody deficiencies (PAD)

Routine monitoring
Putative extrapulmonary predictors of GLILD (splenomegaly, autoimmunity, liver disease, B-cell flow-cytometric typing according to EUROclass trial) are routinely assessed in all PAD patients and reported in the medical record
Spirometry before and after bronchodilator administration (eventual methacholine challenge test) at diagnosis and annually
*D*LCO measurement annually
Blood gas analysis as conventionally indicated
HRCT: at diagnosis (if not recently performed) and every 5 years. HRCT is part of the initial evaluation aimed to a tailored therapeutic approach that includes the choice of Ig replacement therapy dosage, route and frequency of administration, the eventual adjunct of an antibiotic prophylaxis and/or need for pulmonary rehabilitation and exercise training
Lung MRI: currently under evaluation as radiation-sparing imaging technique [142, 143]
Acute infection
Sputum examination or bronchoalveolar lavage may be useful for a precise microbiological diagnosis, in order to drive optimal antibiotic treatment
Waiting for a defined diagnosis, a broad-spectrum oral antibiotic course is prescribed, according to personal history of allergy, previous evidence of antibiotic resistance and eventual ongoing macrolide prophylaxis
Obstructive lung disease
Patients are usually prescribed a combined steroid/LABA topical treatment
In case of bronchiectasis documented by HRCT, prophylactic azithromycin is prescribed (250 mg per day, three consecutive days per week)
Pulmonary rehabilitation and exercise training are recommended to patients displaying bronchiectasis on HRCT scan
Bronchoalveolar lavage (*e.g.* lobar lavage) may also be a mechanistic therapeutic adjunct in selected patients with bronchiectasis
ILD suspicion (cough, dyspnoea on exertion, *D*LCO reduction, restrictive PFT pattern)
6MWT as first choice exercise testing
HRCT scan repetition
If signature of ILD emerging, records are discussed during the ILD MDT meeting
Bronchoscopy is in most cases the first invasive step, both for microbiology and BALF cytology, with lymphocytes sub-population analysis if lymphocytosis is reported
A trans-bronchial biopsy or mediastinoscopy is considered if a lymphoproliferative disease has to be ruled out
Open lung or VATS biopsy is performed if a specific treatment has to be established. In case of signs or symptoms of extrapulmonary disease, PET/CT or PET/MRI imaging is performed, in order to assess different organ involvement and provide alternative sites for a bioptic approach
Treatment: asymptomatic patients may undergo improvement of IgG replacement level, aiming at higher trough levels, even without a previous surgical lung biopsy. In case of concomitant bronchiectasis, prophylactic azithromycin is prescribed, if not already ongoing. Symptomatic patients are started on steroid treatment (20–40 mg of prednisone, as for sarcoidosis). If first-line treatment fails or steroids are contraindicated, combined rituximab-azathioprine treatment is prescribed

GLILD: granulomatous-lymphocytic interstitial lung disease; *D*LCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; Ig: immunoglobulin; MRI: magnetic resonance imaging; LABA: long-acting β-agonist; PFT: pulmonary function test; 6MWT: 6-min walk test; ILD: interstitial lung disease; MDT: multi-disciplinary team; BALF: bronchoalveolar lavage fluid; VATS: video-assisted thoracoscopic surgery; PET; positron emission tomography; CT: computed tomography.

signs of airway disease and ILD are common, despite appropriate IgG replacement therapy, and do not correlate to PFTs [139].

It has been suggested recently that lung magnetic resonance imaging (MRI) might be a viable and radiation-sparing alternative to HRCT in the follow-up of non-CF bronchiectasis patients [140, 141]. This has also been specifically investigated in PID cohorts, in which Lung MRI resulted to be non-inferior to HRCT in identifying most bronchial and parenchymal abnormalities [142, 143]. 1.5 tesla MRI performance has been found to be weaker than HRCT at detecting certain specific lung features (bronchiectasis extension and peripheral airway abnormalities). 3 tesla MRI has been suggested as an accurate and reliable imaging modality [141, 143]. The role of metabolic imaging (FDG-PET/CT) has already been described in GLILD.

Table 3 summarises how we monitor and manage lung disease in PAD at our PAD and ILD referral center (Dept of Medicine – DIMED, University of Padova, Italy and Medicina Interna I, Ca' Foncello Hospital, Treviso, Italy).

Conclusion

Lung disease is a common and relevant clinical feature of PAD. Thus, future studies and a higher and broader degree of awareness of epidemiological and aetiological relationships between PAD and specific pulmonary manifestations are warranted. These will have a strong impact on diagnostic delay, quality of life and long-term prognosis of PAD patients.

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