The Lung in Dysregulated States of Humoral Immunity

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Keywords

Common variable immunodeficiency · IgG4 · Amyloidosis · Lung · Humoral immunity · Light-chain deposition disease

Abstract

In common variable immunodeficiency, lung manifestations are related to different mechanisms: recurrent pneumonias due to encapsulated bacteria responsible for diffuse bronchiectasis, diffuse infiltrative pneumonia with various patterns, and lymphomas, mostly B cell extranodal non-Hodgkin type. The diagnosis relies on significant serum Ig deficiency and the exclusion of any primary or secondary cause. Histopathology may be needed. Immunoglobulin (IgG) replacement is crucial to prevent infections and bronchiectasis. IgG4-related respiratory disease, often associated with extrapulmonary localizations, presents with solitary nodules or masses, diffuse interstitial lung diseases, bronchiolitis, lymphadenopathy, and pleural or pericardial involvement. Diagnosis relies on international criteria including serum IgG4 dosage and significantly increased IgG4/IgG plasma cells ratio in pathologically suggestive biopsy. Respiratory amyloidosis presents with tracheobronchial, nodular, and

cystic or diffuse interstitial lung infiltration. Usually of AL (amyloid light chain) subtype, it may be localized or systemic, primary or secondary to a lymphoproliferative process. Very rare other diseases due to nonamyloid IgG deposits are described. Among the various lung manifestations of dysregulated states of humoral immunity, this article covers only those associated with the common variable immunodeficiency, IgG4-related disease, amyloidosis, and pulmonary light-chain deposition disease. Autoimmune connective-vascular tissue diseases or lymphoproliferative disorders are addressed in other chapters of this issue.

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Previous articles in this series: 1. Lazor R, Nicod LP: The lung in rare systemic diseases. *Respiration* 2017;94:1. 2. Tran C, Barbey F, Lazor R, Bonafé L: Pulmonary involvement in adult patients with inborn errors of metabolism. *Respiration* 2017;94:2–13. 3. Borie R, Wislez M, Antoine M, Cadranel J: Lymphoproliferative disorders of the lung. *Respiration* 2017;94:157–175. 4. Dupuis-Girod S, Cottin V, Shovlin CL: The lung in hereditary hemorrhagic telangiectasia. *Respiration* 2017;94:315–330.

Table 1. Criteria for a probable diagnosis of common variable immunodeficiency adapted from the European Society of Immunodeficiency Registry [5]

Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
<p><i>At least one of the following</i></p> <ul style="list-style-type: none">– Increased susceptibility to infection– Autoimmune manifestations– Granulomatous disease– Unexplained polyclonal lymphoproliferation– Affected family member with antibody deficiency <p>AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2 SD of age-related normal value);</p> <p>AND at least one of the following:</p> <ul style="list-style-type: none">– Poor antibody response to vaccines– Few switched memory B cells (<70% of age-related normal value) <p>AND exclusion of secondary causes of hypogammaglobulinemia^a</p> <p>AND diagnosis established after the 4th year of life (but symptoms may precede)</p> <p>AND no evidence of profound T-cell deficiency^b</p>	<p>For patients <4 years old or patients with incomplete criteria consider “unclassified antibody deficiency”</p> <p>For patients with evidence of profound T-cell deficiency, consider unclassified combined immunodeficiencies</p>

^a Other causes of hypogammaglobulinemia, such as primary immunodeficiency syndromes (e.g., X-linked agammaglobulinemia, hyper-IgM Good’s syndrome) and secondary causes of hypogammaglobulinemia (protein loss enteropathy, nephrotic syndrome, Good’s syndrome, drug, lymphoid, etc.) [3, 4, 8] must be excluded. ^b According to Bertinchamp et al. [6].

Lung Manifestations in Common Variable Immunodeficiency

Common variable immunodeficiency (CVID), a group of disorders [1], is characterized by a loss of B-cell function with low levels of IgG <5 g/L [2, 3] and IgA, with various IgM levels, associated with defective antibody responses [4]. The primary and secondary causes of hypogammaglobulinemia should be excluded as in profound T-cell deficiency. Recently, national and international medical societies have specified diagnostic criteria [3, 5–7] (those from European Society for Immunodeficiencies [ESID] are shown in Table 1) [5]. With an overall prevalence between 1/25,000 and 1/50,000 [8, 9], CVID is less common among Asians and rare among Blacks [2, 10]. CVID is mostly diagnosed in 20- to 40-year-old adults with a male/female ratio of 1 [2, 4, 11], while a first peak, particularly in males, is observed before the age of 10 [11]. A delay of 4–5 years in diagnosis is common [11]. No cause has been established except an autosomal dominant inheritance in some patients [12–14]. The common immune defect in CVID is a loss in B cell function either intrinsic or resulting from T cell defects in their collaboration for antibody production, which results in a reduction in isotype-switched B and plasma cells in bone mar-

row and mucosal tissues [15]. Recurrent naso-sinusal and pulmonary infections by encapsulated bacteria (*Haemophilus influenza* and *Streptococcus pneumoniae*) are the most frequent presentations [2, 16]. CVID may be associated with autoimmune features (particularly cytopenia) in 20–68% of cases, lymphocytic infiltration, and malignancy (lymphoid or solid tumors) [1, 11, 16–18]. These noninfectious complications increase significantly the mortality and morbidity, and impact quality of life [1, 16, 19].

Bronchiectasis in CVID is a common complication of recurrent pneumonia [20] with an estimated prevalence of 23% [11]. The risk of developing bronchiectasis increases with diagnostic delay [11], age [21], complete IgA or IgM deficits, a decreased number of blood memory B cells, a low number of CD4+ T cells, and low circulating mannose binding lectins levels [11, 21–23]. At baseline, chest computed tomography (CT) and pulmonary function tests (PFTs) are recommended [7]. Bronchiectases are cylindrical, bilateral and diffuse, and preferentially located in middle and lower lobes [24, 25]. Bronchial thickening might be due to bronchial inflammation preceding the development of bronchiectasis [25]. Bronchiectasis may lead to *Staphylococcus aureus*, or *Pseudomonas aeruginosa* infection, hemoptysis and respiratory failure. If as-

sociated with functional or parenchymal abnormalities, bronchiectasis predicts poor outcome [16]. In addition to immunoglobulin (IgG) replacement, the treatment of bronchiectasis in CVID is the same as for any other cause [7]. Sputum clearance respiratory physiotherapy, inhaled corticosteroid $\pm$ long-acting beta-agonists [26] and long-term antibiotic prophylaxis with azithromycin [27] may be useful. Inactivated influenza vaccine is recommended [7, 28]. IgG replacement must use high doses (0.6 g/kg/month) [7, 29] as high rates of respiratory infections and poor outcome are associated with suboptimal IgG replacement [11, 29, 30]. Some patients may nevertheless develop bronchiectasis despite IgG replacement therapy [31]. In practice, early diagnosis and prompt initiation of IgG replacement can prevent lower respiratory tract infections and bronchiectasis [32, 33].

Various interstitial lung diseases (ILD) have been observed in CVID (CVID-ILD): lymphoid interstitial pneumonia, organizing pneumonia, granulomatous lung disease, hypersensitivity pneumonitis, or malignancy such as lymphoma [34, 35]. Granulomatous lymphocytic ILD (GLILD) encompasses granulomatous and lymphoid infiltration [34, 36]. Lung granulomatosis may be part of a systemic granulomatosis with extrathoracic involvement simulating sarcoidosis [37–39]. However, extrathoracic granulomas do not predict the granulomatous nature of the associated ILD [40]. Patients with GLILD usually present with dyspnea, cough, and crackles [34, 37]. The prevalence of GLILD among CVID patients is approximately 10–15% [32, 41]. The average delay between CVID diagnosis and GLILD detection is 7.8 years [32, 38, 42]. A restrictive profile at PFTs is observed with reduced carbon monoxide diffusion capacity (DLCO) [43]. Bronchoalveolar lavage (BAL) is useful for investigating infections, while GLILD has been associated with BAL lymphocytosis ($>20\%$) with a variable CD4/CD8 ratio [37, 44]. Granulomatous disease frequently affects the liver, spleen, and skin [37–39]. Immune thrombocytopenia or hemolytic anemia, splenomegaly, polyarthritis, a decrease in switched memory B cells, high blood CD4/CD8 T cell ratio, and high serum IgM may help identify patients with GLILD [21, 32, 34, 45]. PFTs and thoracic CT at baseline plus every year for PFTs and every 5 years for CT are recommended in CVID-ILD [7, 46]. ^{18}F FDG-PET/CT shows an increased uptake in lungs or extrathoracic organs [47]. Lung MRI with diffusion may be useful for detecting bronchial and parenchymal abnormalities for long-term follow-up [48]. On CT, GLILD shows diffuse reticulations, ground-glass opacities and consolidation, with lower lobe predominance [32, 34] (Fig. 1). Me-

Fig. 1. Thoracic computed tomography of a patient with a CVID showing nodules, ground glass opacification micronodules, bronchiectasis, and reticulation with a lower lobe predominance.

diastinal lymphadenopathy, micronodules, interlobular septal thickening, and cysts are also seen in CVID-ILD [32, 49, 50]. Contrary to sarcoidosis, nodules, air bronchogram, halo sign, and bronchiectasis are frequent in CVID-associated granulomatous disease with no perilymphatic predominant distribution of micronodules [37]. The prognosis of GLILD is poor, with median survival of 13.7 years versus 28.8 years in CVID without GLILD [1, 34]. Suboptimal IgG replacement, elevated IgM, and severe thrombocytopenic episodes lead to a higher risk of progressive disease [51]. Immunomodulatory treatments may be beneficial to some patients [51]. Immunosuppressive agents expose to infectious and malignant diseases. Monitoring corticosteroid-induced CD4 lymphopenia and pneumocystis prophylaxis are recommended [46]. Despite weak evidence of efficacy, corticosteroids may be used as first-line therapy [38]. Immunosuppressive steroid-sparing agents showed variable success. The azathioprine and rituximab combination was found effective in a small series of GLILD patients, with improved spirometry and imaging [41]. For prominent T cell infiltration, corticosteroids with or without cyclosporine have been successful [52]. Infliximab has also been successful for granulomatous disease in case reports [53]. Lung transplantation should be considered in the case of refractory progressive disease [54]. The incidence of malignancy is increased in CVID, particularly lymphoma,

which occurs in up to 3–8% of patients [11, 16]. Lymphomas are more common in patients aged between 30 and 60 years and in females [13, 16]. They usually are B cell extranodal non-Hodgkin lymphomas [16, 55]. Genetic aberrations, chronic infection, and immune dysregulation [56, 57] are suggested to explain the increased lymphoma incidence. Lung mucosa-associated lymphoid tissue (MALT) has been reported, occasionally related to *Helicobacter pylori* [58, 59]. At CT, MALT lymphomas manifest as chronic localized opacities including consolidations, nodules, and masses with the presence of airways within the lesions in 85% [60, 61]. After respiratory failure, lymphoma is the second cause of death in CVID [16].

IgG4-Related Respiratory Disease

Since the initial report of a patient with sclerosing cholangitis associated with an elevated serum IgG4 concentration [62], IgG4-related disease (IgG4-RD) has been defined as a multiorgan chronic fibroinflammatory condition characterized by lymphoplasmacytic infiltrates with abundant IgG4 plasma cells, associated with storiform fibrosis and often high serum IgG4 concentrations [63, 64]. Fibroinflammatory lesions may virtually affect every organ [63]. Presentation is highly diverse, including autoimmune pancreatitis, sialadenitis, dacryoadenitis, lymphadenopathy, periaortitis/retroperitoneal fibrosis and tubulointerstitial nephritis [64, 65]. Uchida et al. [66] estimated the annual incidence and prevalence of IgG4-RD in Japan to be 0.28–1.08/100,000 and 6/100,000, respectively. IgG4-RD affects middle- to old-age (median age: 50.3–67) subjects, with a male/female ratio ranging from 1.6:1 to 4:1 [63, 67, 68]. IgG4-RD immunopathogenesis remains incompletely elucidated. It includes oligoclonal expansion of plasmablasts as well as CD4+ T cytotoxic cells [69–71]. Oligoclonal expansion of circulating CD19+CD20–CD27+CD38+ plasmablasts reflects the disease activity [72]. The implication of IgG4 is uncertain as they have noninflammatory properties in contrast with other IgG subclasses [69, 73]. IgG4 increase might represent an ineffective attempt to downregulate the ongoing primary inflammatory response triggered by still unknown antigens. However, IgG4 might be pathogenic through interaction with circulating lectins to activate complement [74]. Neither causal antigens nor at risk occupational exposure has been identified so far [75].

Since the first report of ILD associated with autoimmune pancreatitis [76], various presentations of intrathoracic IgG4-RD have been described: ILD, lung nodules,

bronchial inflammation, mediastinitis, and pleuritis [64, 65, 77, 78]. IgG4-related respiratory disease (IgG4-RRD) has been proposed to refer to pulmonary and other intrathoracic organ involvement [79]. Thoracic manifestations are estimated to represent 13–35% of all IgG4-RD [67, 68, 80–83].

These may occur in isolation [84] in 20% of patients [68] but most often accompany 2 or more extrapulmonary localizations [75, 81, 85]. Extrapulmonary manifestations may be synchronous or metachronous with those affecting the lung [86]. IgG4-RD presentation typically includes 5–10 kg weight loss and fatigue for months or even years before diagnosis [64]. While fever is unusual in IgG4-RD, it might be more frequent in patients with intrathoracic involvement [85]. Many patients with or without intrathoracic involvement have ear, nose, and throat symptoms [64], especially in the absence of atopy [87]. Thoracic symptoms include cough, hemoptysis, dyspnea, and chest pain [84, 86]. However, half of the patients are asymptomatic [85, 86]. Four main CT pulmonary patterns of IgG4-RRD have been reported [86]: (i) solitary solid nodule or mass, (ii) bronchovascular bundles and interlobular septa thickening, (iii) alveolointerstitial pattern showing honeycombing, bronchiectasis, and diffuse ground glass opacities (GGO) with possible multiple small nodules, (iv) less frequently multiple round-shaped GGO [85]. Consolidations and bronchiolitis have also been reported [84, 88, 89]. Enlarged lymphadenopathy is present in half of the cases [85, 86]. Often asymmetrical or solitary [85], it may be similar to sarcoidosis [90, 91]. Fibrosing mediastinitis [92, 93], nodular lesions, or pleura thickening may be seen [85, 86]. Although rare, pericardial effusion or thickening [85] may lead to constrictive pericarditis or cardiac tamponade [94]. All these lesions may be associated (Fig. 2).

¹⁸F-FDG-PET/CT is considered very helpful to guide biopsy and monitor treatment [95]. The characteristic pattern of ¹⁸F-FDG uptake in IgG4-RD is a symmetrical distribution in the salivary glands, diffuse in the enlarged pancreas without duct obstruction, patchy in the aorta wall or in retroperitoneal lesions [95].

PFTs are often normal, but obstructive or restrictive profiles [75] or decreased diffusion capacity may be observed [78]. Pulmonary hypertension (PH) caused by obliterative phlebitis due to IgG4-positive plasma cell infiltration has been reported [96].

Measurement of serum IgG4 concentration evaluation is important in the workup and outcome assessment of IgG4-RD patients, but a level >135 mg/dL is neither necessary nor sufficient for diagnosis [97]. Around 50% of

Fig. 2. Thoracic computed tomography of a patient with IgG4-related lung disease showing thickening of bronchovascular bundles, interlobular septa, nodule and consolidation, reticulation, and asymmetrical hilar lymphadenopathy.

patients have normal serum IgG4 concentrations [67], but response to treatment in the case of active disease is better when serum IgG4 is increased [67]. High serum IgG4 levels may be seen in carcinomas and autoimmune diseases [98]. An increase in C-reactive protein or Krebs von den Lungen-6, low level of complement and antinuclear antibodies and/or rheumatoid factor positivity may be observed [76, 79, 85, 99]. Blood eosinophilia and elevated IgE level especially without atopy, suggest an IgG4-RD process [87]. IgG4 and C-reactive protein levels are higher in patients with intrathoracic disease [85]. BAL in IgG4-RD predominantly shows lymphocytosis with a normal CD4/CD8 ratio [75]. BAL total cell counts and

lymphocyte rates are significantly lower with significantly more eosinophils, and cytokines characteristic of Th2 response than in sarcoidosis [90]. Histopathology combined with immunohistochemistry remains the cornerstone of diagnosis (Fig. 3). Even though needle biopsy has been generally considered inadequate for confirming IgG4-RD diagnosis [100], the diagnostic yield of trans-thoracic core needle biopsy reaches 2/3 of the cases [84]. However, surgical lung biopsy is often needed [84]. An international pathological consensus statement defined IgG4-RD diagnosis on the combined presence of a characteristic histopathological pattern and increased numbers of IgG4⁺ plasma cells [101] (Fig. 3). The 3 main pathological features are dense lymphoplasmacytic infiltration, obliterative phlebitis, and a storiform fibrosis pattern defined as radially arranged collagen fibers that seem to weave through the tissue [64, 101], with occasional eosinophilic infiltration [86]. Lesions may have a lymphatic distribution [75, 102]. Epithelioid cell granulomas and prominent neutrophilic infiltrate are considered inconsistent with IgG4-RD diagnosis [101]. Some variants make the diagnosis more difficult [77, 86, 101]: neutrophil aggregates in bronchioloalveolar spaces, multinucleated giant cells [86], obliterative arteritis rather than phlebitis [86], absence of storiform fibrosis [101]. After a long course, fibrosis may predominate, making histological features less specific [64]. Pleura may be severely thickened by diffuse sclerosing inflammation [86]. The IgG4 immunostaining is essential, showing a polyclonal lymphoplasmacytic infiltration rich in IgG4⁺ plasma cells. Diagnosis requires an increased IgG4⁺/IgG ratio over 40% with an elevated number of IgG4⁺ plasma cell/high power field in the biopsy [101]. IgG4⁺ plasma cells are diffusely distributed within nodular lesions in the alveolar interstitium, bronchovascular bundles, interlobular septa, and pleura [86, 101]. Focal aggregations are atypical [64]. The appropriate cut-off for IgG4 plasma cell counts may vary from organ to organ and according to the importance of fibrosis [101]. IgG4-RD should not be diagnosed only based on IgG4 plasma cell accumulation as it can also occur in a large wide of inflammatory conditions (Castleman disease, collagen disease-related lung disease, vasculitis, Rosai-Dorfman disease), lymphomas, or lung cancer [79, 101, 102]. Association with other patterns has been reported including usual interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia, and granulomatosis with polyangiitis [75, 103–105]. In summary, the most accurate assessment of IgG4-RD is based on a full clinical history, physical examination, laboratory investigations, and appropriate imaging studies.

Fig. 3. Hematoxylin-eosin stain (**a**, **b**, **d**) and IgG4 immunostaining (**c**) of a surgical lung biopsy of a pulmonary nodule from a patient presenting nodules, mediastinal adenopathy, and interstitial pneumonitis on chest computed tomography. **a** Low power field ($\times 50$) showing a dense inflammatory infiltrate in a peribronchiolar area. **b** Plasma cell infiltration is observed around a bronchiole ($\times 100$). **c** IgG4-positive plasma cells (arrows) surrounding a bronchiole (*) ($\times 100$). **d** Mononuclear cell infiltration surrounding a pulmonary artery with plexiform lesions.

Confirmation by biopsy is strongly recommended to exclude malignancies and other IgG4-RD mimics [100]. Comprehensive diagnostic criteria for IgG4-RD have been proposed in Japan for nonspecialists [106], and recently Matsui et al. [79] adapted these criteria for specific diagnosis of IgG4-RRD (Table 2).

An international consensus for IgG4-RD treatment has recently been published [100]. Patients with either symptomatic active IgG4-RD or asymptomatic patients with specific risks require to be treated to prevent irreversible sequelae in the biliary tree, kidney, aorta, mediastinum, retroperitoneum, and mesentery. Emergency

treatment is needed for those at risk for aortic dissection, ureteral obstruction, renal failure, common bile duct compression, visual acuity reduction, nerve palsies, and pericardial complications [100]. Surveillance is advocated in asymptomatic patients with localized disease without risky outcome [107]. Glucocorticoids are given first to obtain remission. In a multicenter phase II prospective trial, 0.6 mg/kg/day prednisolone was administered initially, then reduced by 10% every 2 weeks followed by a maintenance dose, allowing a complete remission in 66% of patients at 1 year [108]. A low maintenance dose of prednisone (5–10 mg/day) is administered to some pa-

tients and recommended for up to 3 years according to some clinicians [109]. Glucocorticoids combined with steroid-sparing immunosuppressive agents (cyclophosphamide [84, 85], mycophenolate mofetil [110], azathioprine, methotrexate) may be advised in some contexts. For relapse after a prior successful remission, a retreatment with glucocorticoids is indicated and, for remission maintenance, a steroid-sparing agent is to be considered [100]. Rituximab [111] appears effective and may be used if there is a contraindication to corticosteroid or in case of corticoreistance, or as a steroid-sparing agent. In one open-label trial, 97% of patients under rituximab responded to treatment response and 47% were in complete remission at 6 months [111]. Corticosteroids trigger a good and rapid response in IgG4-RRD with improvement after 2 weeks to several months [64, 112]. Spontaneous improvement has occasionally been reported in the lung [75, 85]. ILD, lymphadenopathy, and bronchial thickening are sensitive to corticosteroids and immunosuppressive treatments, while one-third of solitary nodular lesions are not [85]. In contrast to idiopathic conditions, fibrosing mediastinitis, PH, even a usual interstitial pneumonia pattern observed on CT or obliterans bronchiolitis related to IgG4 respond well to treatment [92, 96, 105, 113]. The long-term outcome and prognosis are not yet known. Death from respiratory failure has been reported [84]. A history of relapse appears to be a strong predictor of further relapse, as well as elevated levels of serum IgG4, IgE, and eosinophils [67]. A poor response should raise the possibility of an alternative diagnosis, particularly cancer [64, 108].

Respiratory Amyloidosis

Amyloidosis is characterized by extracellular aggregates of insoluble misfolded fibrils leading to organ dysfunction [114]. In the consensus terminology, A designates “amyloidosis” followed by indicators of the specific protein precursor: IgG-associated AL amyloidosis (L: light chains), serum amyloid A amyloidosis (AA) associated with chronic inflammatory diseases, transthyretin amyloidosis (ATTR) with accumulation of transthyretin (mutant in hereditary form, or acquired in senile form), and β_2 -microglobulin accumulation amyloidosis (AB2M) in dialyzed patients [114]. More frequently primitive, amyloidosis may be associated with another disease. AL amyloidosis (immunoglobulinic or “primary” amyloidosis) is by far the leading type of amyloidosis in the respiratory system, while AA amyloidosis is much rarer [115, 116].

Table 2. Diagnostic criteria for IgG4-related respiratory disease (adapted from Ryu et al. [78])

<i>A Diagnostic criteria</i>	
I	<p>Chest imaging</p> <p>Imaging findings include any of the following intrathoracic lesions: hilar/mediastinal lymphadenopathy, bronchial wall/bronchovascular bundle thickening, interlobular septal wall thickening, nodular shadow, infiltrative shadow, pleural thickening and/or effusion</p>
II	<p>Serology</p> <p>Elevated serum IgG4 concentration of ≥ 135 mg/dL</p>
III	<p>Histology</p> <p>Two or more of the following items are required for intrathoracic tissues analysis:</p> <p>a: ≥ 3 items; b: 2 items</p> <ol style="list-style-type: none"> 1 Marked lymphoplasmacytic cell infiltration of peribronchovascular bundles, interlobular septa, and/or pleura 2 IgG4⁺/IgG plasma cell ratio $>40\%$ and/or >10 IgG4⁺ cells/high power field 3 Obliterative phlebitis or arteritis 4 Storiform fibrosis or proliferation of spindle-shaped cells around infiltrating lymphocytes
IV	<p>Other organ involvement</p> <p>Presence of extrathoracic lesions satisfying the criteria of IgG4-related disease as sclerosing dacryoadenitis/sialadenitis, auto immune pancreatitis, sclerosing cholangitis, IgG4-related kidney disease, and retroperitoneal fibrosis</p>
V.	<p>Biological test results</p> <p>Hypocomplementemia</p>
<i>B Diagnosis</i>	
1	<p>Definite: I + II + IIIa, or I + II + IIIb + IV</p> <p>Definite (histological): I + all the 4 items of III</p>
2	<p>Probable: I + II + IV, or I + II + IIIb + V</p>
3	<p>Possible: I + II + IIIb</p>
<i>C Differential diagnosis</i>	
<p>It is important to differentiate IgG4-related respiratory disease from diseases with similar features: Castleman disease (plasma cell type), collagen disease-related lung disease, granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), sarcoidosis, respiratory organ infection, Rosai-Dorfman disease, inflammatory myofibroblastic tumor, malignant lymphoma, lung cancer</p>	

AL amyloidosis is most commonly found in a context of plasma cell disorder, while 5% concern B-cell lymphoma. All structures of the respiratory system may be affected: airways, parenchyma, pleura, intrathoracic lymph nodes, and vessels [116, 117]. Lesion distribution varies accord-

Table 3. Respiratory tract amyloidosis patterns

	Tracheobronchial amyloidosis	Parenchymal amyloidosis	Diffuse interstitial amyloidosis
Main subtype	Localized AL	Localized AL	Systemic AL
Phenotype	Obstructive bronchial disease	Nodular lesions ± calcifications Cystic lesions	Alveolar-septal involvement Thickening of interalveolar septas Parenchymal nodules
Underlying disease	No	Low-grade lymphoma Connective tissue disease Neoplasia	Low-grade lymphoma Multiple myeloma Connective tissue disease

ing to the localized or nonlocalized nature of amyloidosis and its subtype (Table 3) [118].

Systemic amyloidosis most often affects lung parenchyma, lymph nodes, and pleura, and may be associated with cardiac or renal involvement. Localized amyloidosis includes tracheobronchial involvement and isolated parenchymal involvement with nodular, cystic, and diffuse interstitial manifestations.

The diagnosis of amyloidosis relies on histopathology [114]. Routine staining shows extracellular deposition of amorphous eosinophilic material especially around vessels. After Congo red staining, a red appearance is observed in normal light and apple-green birefringence under cross-polarized light. Amyloid deposits may show a red-violet metachromasia with violet crystal and a strong fluorescence with thioflavin under UV light [114]. In contrast to the granular deposits of light chains, amyloid deposits are ultrastructurally characterized by 8- to 10-nm diameter fibrils [114]. Immunodetection of kappa/lambda light chains, serum amyloid A, transthyretin, and apolipoprotein A1 is helpful. Negative immunostaining for SAA and TTR exclude AA and TTR types, but negative immunostaining for kappa and lambda chains may occur in up to 60% of AL type [119]. Mass spectrometry is becoming the gold standard for typing amyloid deposits [120].

Tracheobronchial amyloidosis (TBA) accounted for 1.1% of cases in a large series of patients with amyloidosis [121], but up to 29–53% of cases of respiratory amyloidosis [121–128]. The mean age is 48–57 without gender predilection [8–15]. TBA may be due to monoclonal gammopathy [129] with or without systemic amyloidosis [130–132]. Light-chain deposits of amyloid may be due to focal clonal plasma cell proliferation responsible for local amyloid production [133, 134]. TBA caused by AL or AA systemic amyloidosis is rare [124, 135, 136]. Associated mediastino-hilar lymphadenopathy may suggest systemic amyloidosis [129].

Bronchoscopy in TBA reveals multifocal submucosal plaques (85%) (Fig. 4) and pseudotumor masses (15%) [128]. Usually isolated, the amyloid tumor-like masses are not obstructive, and the diagnosis is often fortuitous (Fig. 4). Conversely, multifocal submucosal plaques with submucosal white-greyish deposits reduce airway lumen and are usually symptomatic – cough, hemoptysis, dyspnea, hoarseness, or recurrent pneumonia; shortness of breath may be the main symptom with sometimes stridor, wheezing, or whistling [121–123, 126, 128, 135–139]. Often mistaken for asthma or COPD, the correct diagnosis may be delayed for many years. Lesions may be exclusively laryngeal (12.5%), tracheal (3%), laryngotracheal (28%), tracheobronchial (44%), or extend to the entire respiratory tract (12.5%) [139]. Compressive amyloid goiter has been reported [140]. PFTs show airflow obstruction or a characteristic upper airway inspiratory obstruction.

Chest radiography unveils atelectasis, possible calcifications, or narrowing of the tracheal lumen [141, 142]. Lung CT may show focal or diffuse circumferential tracheal and bronchial thickening with luminal narrowing, atelectasis, and/or localized bronchiectasis [121, 142]. Calcifications with “ossification of submucosal nodules” may be observed. Three-dimensional reconstruction allows precise lesion mapping [143]. Narrowband imaging bronchoscopy might be more sensitive for early diagnosis [144].

Surgical excision of the lesions is now abandoned due to a high risk of hemorrhage. Endoscopic debulking yields satisfactory long-term results. Nd-YAG laser, argon plasma coagulation, freezing, resection, clamping, microwaving, high-frequency electrocautery, and stent implantation under rigid bronchoscopy may be used [145]. Repeated procedures ensure good bronchial permeability [146]. In limited series, targeted external radiotherapy (20 Gy in 10 fractions) led to clinical improvement within a

Fig. 4. Endoscopic presentation of tracheobronchial amyloidosis: evidence of multifocal submucosal plaques.

period of 1 month to 1 year [147, 148] with long-term improvement of spirometry [149]. Combined endoscopic procedures may be followed by radiotherapy [150]. Interesting results with colchicine have been reported [151]. TBA outcome may be marked by recurrent pneumonia and progressive obstructive respiratory failure. In contrast to other localized forms of amyloidosis, TBA has a bad prognosis with an estimated 5-year survival of only 30–50% [142].

Nodular and cystic amyloidosis accounts for 44–58% of respiratory amyloidosis [122, 123, 126, 128, 152–154]. Cystic lesions are uncommon and often associated with nodules [155]. The mean age at diagnosis is 67 years, and the male/female ratio is 3:2 [116, 126, 156].

Mostly discovered incidentally on thoracic imaging or autopsy, nodular amyloidosis may also be revealed by cough, dyspnea, or hemoptysis. Amyloidosis should be considered in the gamut of multicystic lung diseases among biopsy-proven pulmonary amyloidosis as a cystic lung pattern is observed in 11% of cases [155].

Nodules may be single (52%) or multiple (48%), with various shapes and sizes [157]. Spots of calcification/osification are found in 26–50% [117, 122] and cavitations in 10% of cases [117, 122, 126]. Peripheral subpleural localization is common, particularly in the lower lobes. Multiple cystic lesions may be associated [158]. Cysts tend to be round or lobulated, multiple and bilateral, of small to moderate size. Most are thin-walled with a lower lobe predominance [155]. In 81% of cases, cysts are associated with nodules, some of which are partially calcified

[155]. An increased ^{18}F FDG uptake [159–162] is frequent [163] with reduced activity on the 2-h delayed images, in contrast to malignant lesions [164]. ^{123}I -serum amyloid P component scintigraphy may be useful to document visceral uptake [165].

Tissue for histopathology may be obtained by trans-bronchial biopsy or CT-guided needle biopsy, but surgical lung biopsy is considered more suitable for amyloid deposit analysis and detection of a clonal B cell proliferation [155, 161, 164, 166].

Nodular and cystic pulmonary amyloidosis may be the only localization of amyloidosis resulting from an underlying lymphoproliferative disorder such as marginal zone lymphoma of MALT lymphoma [167]. AL amyloidosis predominates in cystic lung amyloidosis [155]. It is mainly a localized pulmonary amyloidosis (76%) and less often associated with systemic amyloidosis (19%) [155]. Fifty-seven percent of patients present an associated connective tissue disease (CTD), generally Sjögren syndrome [155, 168]. Localized amyloidosis must be distinguished from B-cell lymphoproliferation with peritumoral amyloidosis [169]. Lung and soft tissues are more commonly affected by both entities [169]. Peritumoral amyloidosis involves a single organ, either lung or soft tissue, associated with MALT lymphoma and trace or undetectable IgM paraprotein [169]. Systemic amyloidosis involves several organs with high IgM paraprotein and underlying Waldenström macroglobulinemia [170–172]. While usually AL, localized parenchymal amyloidosis may be AA, wild-type ATTR, mixed AB2M/AL amyloidosis and, exceptionally, senile [116].

Localized pulmonary nodular amyloidosis is usually associated with a benign prognosis, rarely requiring treatment. Conservative excision may be curative with exceptional postoperative recurrences [173]. Fatal hemoptysis is a rare event [174]. Peritumoral amyloidosis is rarely progressive, despite the lack of appreciable response [158, 167, 169]. By contrast, shortened survival was reported in patients with IgM-related systemic amyloidosis as a complication of cardiac or renal involvement [169, 171, 172]. These observations justify comprehensive evaluation to distinguish peritumoral amyloidosis from systemic AL, as the therapeutic approach is different [175].

Interstitial amyloidosis with diffuse alveolar septal deposits may be part of a systemic process or limited to lungs, the latter being exceptional and severe [122, 125, 128]. The high prevalence of lung involvement in systemic AL amyloidosis contrasts with its low clinical impact [124, 126, 152, 176]. Interstitial involvement is exceptionally due to AA amyloidosis [115, 177]. While antemortem

Fig. 5. Thoracic high-resolution computed tomography. Amyloidosis with diffuse interstitial lung disease: nodules, septal lines, consolidation, pleural nodules, and thickening.

diagnosis is rare [176], chest radiographs obtained within 1 year before death are abnormal in 91% of cases and chest CT in 97%. Lung involvement in ATTR amyloidosis is always associated with cardiac amyloidosis [176].

Interstitial amyloidosis may alter alveolar-capillary gas exchange leading to fatal respiratory failure in 50% of cases. Underlying condition may be a lymphoproliferative disorder or a CTD. IgM as IgG-related amyloidosis usually occurs in the setting of monoclonal disorders with a low tumor burden [171]. The diagnosis of lung involvement in AL amyloidosis [118, 178] relies on an interstitial pattern on CT and histopathology. Interstitial amyloidosis is more frequent in IgM amyloidosis mostly of kappa light chain [171, 179], while it represents a minority among all amyloidoses [180]. Most often (52%), the underlying disease is a lymphoproliferation rather than myeloma [170].

CT shows diffuse irregular lines, thickening of interlobular septa with possible honeycombing and bronchiectasis (Fig. 5). Parenchymal nodules and/or cystic lesions and mediastino-hilar lymphadenopathy may be associated [141, 181]. Sometimes, a diffuse micronodular pattern may be observed [141, 182, 183]. Areas of septal thickening, predominantly peripheral and basal consolidation, patchy GGO and parenchymal micronodules are all compatible with interstitial amyloidosis [184] (Fig. 5).

Pulmonary progression is generally slow in CTD-associated amyloidosis, but may be rapid in systemic amyloidosis, making it the second cause of death after cardiac

involvement [176]. The main respiratory causes of death include pneumonia, aspiration, and pulmonary embolism, but rarely amyloidosis itself [176]. In the largest series of IgM-related amyloidosis, the median overall survival was 47.9 months. Patients free of bone marrow clonal infiltrate have a better survival (54 months) than those with lymphoid (44 months) or plasma cell (23 months) infiltrate. A worse response to novel treatment agents is observed in IgM compared to IgA and/or IgG AL amyloidosis [170].

Pulmonary vascular amyloid deposition is frequent, particularly in systemic amyloidosis with cardiac involvement. Mostly asymptomatic, it may rarely be responsible for hemoptysis, hemothorax, or even intra-alveolar hemorrhage with sometimes fatal hemorrhagic diathesis [174, 185]. PH during AL amyloidosis is mostly secondary to restrictive amyloid cardiomyopathy. Exceptional cases of isolated precapillary PH have been described [186–190].

Pleural amyloidosis, almost exclusively of the AL type, is very rare, representing only 5–10% of respiratory amyloidosis [121]. Pleural effusion ranges from transudate in relation to cardiac or renal involvement or dysthyroidism to exudates associated with specific pleural amyloid involvement. Chylothorax, either related or not to compressive intrathoracic lymphadenopathy, has been reported [191]. Imaging may show pleural thickening and calcifications [192]. Pleural effusion confers a bad prognosis with an estimated median survival of 1.6 months in the case of cardiac amyloidosis [191].

Mediastinal and hilar lymph nodes may be calcified (in eggshell) and often associated with parenchymal or TBA [193]. In systemic amyloidosis, enlarged mediastinal lymph nodes may be localized and isolated in 17% of cases or more frequently associated with pulmonary involvement [183, 194]. Primary AL amyloidosis may be diagnosed on lymphadenopathy by endobronchial ultrasound-guided transbronchial needle aspiration cytology (EBUS) [195–198].

Pulmonary Light-Chain Deposition Disease

Historically described in the kidney, light-chain deposition disease (LCDD) may exceptionally affect the lung [199]. An amorphous eosinophilic material, not stained by Congo red, is distributed in the interstitial space along the basal membrane and corresponds to the deposition of monotypic (most often kappa) light chains [199]. Kidney, heart, and digestive tract are by far more often involved. Mostly associated with lymphoproliferation, LCDD may

be associated with autoimmune conditions or may be idiopathic. Isolated pulmonary LCDD is sparsely reported [156, 200–202]. Manifestations include nodular and diffuse interstitial patterns [203]. Cystic forms of LCDD have recently been described [201, 203]. Patient age ranges from 33 to 78 years, with a mean of 60.7 years and a male/female ratio of 1:2. The differential diagnoses include other multicystic lung diseases [204]. Bronchial light chain deposits have also been associated with bronchiectasis or tracheomegaly [181, 205, 206]. Deposits may be detected on labial biopsies [201]. End-stage multiple cystic lung disease requiring lung transplantation has been described [201]. Most commonly, LCDD is associated with myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia or other malignant B-cell lymphoproliferation [203]. Plasma B cell dyscrasia should therefore be systematically screened in serum, urine, or by bone marrow aspiration. In one-third of cases, failure to detect a systemic B-cell clone suggests a primary in situ pulmonary plasma cell proliferation. Combined with clinical and biological data, the data of Colombat et al. [206] support an antigen-driven primary pulmonary lymphoproliferative disorder. Pulmonary LCDD is an indolent or slowly progressive disease [203]. No recurrence after a 4-year follow-up was observed after lung transplantation [201, 207]. Unlike localized disease, treatment of systemic LCDD aims at reducing the serum free light chain level to limit lung deposits. Optimal treatment remains to be defined. Chemotherapy can be associated with peripheral blood stem cell transplantation [207].

Other Diseases due to Nonamyloid IgGs

Heavy-Chain Deposition Disease

Heavy-chain deposition disease confined to the respiratory tract is extremely rare consisting of parenchymal masses and enlarged lymph nodes [208].

Crystal Globulinemia

Due to unknown mechanisms, crystal formation by monoclonal Ig, particularly kappa light chains, is virtually possible in every tissue. Pulmonary involvement may be interstitial or nodular with pleura more rarely involved. Lesions are characterized by infiltration of histiocytic cells containing crystal deposits [209–212]. The underlying lymphoid B proliferation may remain occult [210].

Cryoglobulinemia and Cryofibrinogenemia

During AL amyloidosis or other IgG deposition diseases, the involved monoclonal Ig may be difficult to detect because of cold-induced precipitation of the protein (type I cryoglobulin). Thus, physicians should carefully look for a cryoglobulin and type it. The clinical presentation, mostly dermatologic, is related to the vascular and capillary tropism of the cryoprecipitates. Its respiratory manifestations may be an organized pneumonia particularly with vascular involvement with abundant siderophages [213]. Cryofibrinogen may be distinguished from cryoglobulin according to tissue granulomatous reaction in the former [214].

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