The lung in amyloidosis

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ABSTRACT   Amyloidosis is a disorder caused by misfolding of autologous protein and its extracellular deposition as fibrils, resulting in vital organ dysfunction and eventually death. Pulmonary amyloidosis may be localised or part of systemic amyloidosis.

Pulmonary interstitial amyloidosis is symptomatic only if the amyloid deposits severely affect gas exchange alveolar structure, thus resulting in serious respiratory impairment. Localised parenchymal involvement may be present as nodular amyloidosis or as amyloid deposits associated with localised lymphomas. Finally, tracheobronchial amyloidosis, which is usually not associated with evident clonal proliferation, may result in airway stenosis.

Because the treatment options for amyloidosis are dependent on the fibril protein type, the workup of all new cases should include accurate determination of the amyloid protein. Most cases are asymptomatic and need only a careful follow-up. Diffuse alveolar-septal amyloidosis is treated according to the underlying systemic amyloidosis. Nodular pulmonary amyloidosis is usually localised, conservative excision is usually curative and the long-term prognosis is excellent. Tracheobronchial amyloidosis is usually treated with bronchoscopic interventions or external beam radiation therapy.

Introduction

Systemic amyloidoses are caused by conformational changes and aggregation of autologous proteins that deposit in tissues in the form of fibrils [1]. This process causes functional damage of the organs involved, and eventually leads to death, if left untreated. With an estimated incidence of ∼10 cases per million person-years [2], systemic amyloidoses are listed among rare diseases. Nevertheless, their annual rate is comparable to that of chronic myelogenous leukaemia and Hodgkin disease [3], which are diseases well known to practising physicians despite their relative rarity.

Almost 15 forms of systemic amyloidoses are known and classified according to the different amyloidogenic precursor proteins [4]. The molecular mechanisms through which different soluble proteins become prone to undergo an irreversible transition from their native conformation into highly ordered

aggregates sharing the unique structural features of amyloid fibrils are diverse [1]. They involve increased synthesis, as in the amyloidosis reactive to chronic inflammation or plasma cell dyscrasias, mutations increasing the propensity to form amyloid in the hereditary amyloidoses and ageing in wild-type transthyretin amyloidosis (ATTRwt), formerly known as senile systemic amyloidosis (table 1).

All amyloid fibrils share a common ultrastructure, irrespective of the precursor proteins, as demonstrated by X-ray diffraction studies [5]. The highly ordered morphology (antiparallel strands perpendicular to the fibril axis) is responsible for the organised binding of Congo red, resulting in green birefringence under polarised light.

Amyloidosis can be systemic (and often lethal if not effectively treated) or localised. The diagnosis of amyloidosis should be based on tissue biopsy. Sampling of easily accessible sites, such as abdominal fat [6] or minor salivary glands [7] can spare organ biopsy in most patients. An increased risk of haemorrhage has been reported with organ biopsy, with <5% bleeding complications in liver biopsies [8] where the transjugular approach should be preferred. The risk of haemorrhage should be considered when performing endobronchial or transbronchial biopsies, particularly in patients with factor IX and X deficiencies [9, 10]. Less invasive procedures, such as fine needle aspiration, have been attempted successfully [11, 12]. Since the clinical characteristics of the different forms of amyloidosis are similar, but treatment differs radically, targeting different precursors and pathogenic mechanisms, the unequivocal identification of the amyloid type is vital to avoid therapeutic errors. Typing of the amyloid deposits can be performed using immunohistochemistry in specialised laboratories [13], immune-electronmicroscopy [6] and mass spectrometry [14, 15].

Mutations in genes coding for amyloidogenic protein variants can be searched using DNA analysis to confirm hereditary forms.

Involvement of the lung is relatively common, but rarely symptomatic. From the pathologist's perspective, amyloidosis can appear in the lung in three different forms: nodular pulmonary amyloidosis, diffuse alveolar-septal amyloidosis and tracheobronchial amyloidosis. Lung diseases characterised by chronic inflammation (e.g. bronchiectasis and cystic fibrosis) can give rise to systemic AA (apolipoprotein serum amyloid A) amyloidosis. Moreover, respiratory manifestations are common in systemic amyloidosis. Finally, amyloid deposits can directly target the lung and respiratory tract.

Nodular pulmonary amyloidosis

Nodular pulmonary amyloidosis is usually localised and an incidental finding on chest radiography. It is defined as one or more nodular amyloid deposits involving the lung. It usually represents localised AL

TABLE 1 Common types of systemic amyloidosis

	Precursor protein	Acquired/ hereditary	Organ involvement	Symptoms and signs	Treatment
Systemic AL	Monoclonal LCs	Acquired; caused by plasma cell clone	All organs (except the brain)	Depend on organ involved	Chemotherapy, ASCT
Localised AL	Monoclonal LCs	Acquired; caused by plasma cell clone	Tracheobronchial tree, lungs, urinary bladder, skin (others)	Depend on location	Localised therapy
ATTRwt	Wild-type transthyretin	Acquired; age-related	Heart, soft tissue, lung	Heart failure	Heart failure therapy (new therapies)
ATTRm	Mutated transthyretin	Hereditary	Heart, PNS/ANS	Heart failure and peripheral neuropathy	Liver transplant (new therapies)
AA	Apolipoprotein serum amyloid A	Acquired; reactive to chronic inflammation	Heart, kidney, liver, lung	Nephrotic syndrome	Treatment of underlying condition

The amyloid types are identified by acronyms where the letter "A" for amyloidosis is followed by the abbreviation of the protein forming the amyloid fibrils. LCs: immunoglobulin light chains; ASCT: autologous stem cell transplant; PNS: peripheral nervous system; ANS: autonomic nervous system.

(immunoglobulin light chain) or AL/AH (mixed immunoglobulin light chain/heavy chain) amyloidosis [16, 17], but rare cases of systemic AL, localised AA, localised ATTRwt and localised Aβ2M/AL (mixed β2-microglobulin/immunoglobulin light chain) amyloidosis have been reported [18–24]. Of note, localised AL amyloidosis is not unique to the lungs and the tracheobronchial tree. Commonly reported sites included urinary tract, larynx, skin and eyelids [25, 26].

The mean age of patients is 67 years, and the male:female ratio is 3:2 [27, 28]. Nodular amyloidosis usually presents with peripheral subpleural localisations of variable size that can be bilateral. Differential diagnosis with neoplasia is needed, but the prognosis of nodular amyloidosis is generally very good. However, larger masses measuring up to 15 cm in greatest dimension have been reported [29]. They grow slowly and unusual cystic radiological features have been described [30].

Many experts now believe that most cases of nodular pulmonary amyloidosis are the result of an underlying lymphoproliferative disorder in the spectrum of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [16]. One study, from the Mayo Clinic [31], reported six cases in which this association could be made without the coexistent systemic amyloidosis. In these patients, the relative paucity of presenting symptoms and physical examination findings, and the absence of systemic amyloidosis after a rigorous clinical evaluation corroborated the localised nature of the amyloid in the pulmonary marginal zone lymphoma. The underlying lymphoproliferative disorder might be subtle, but sensitive methods reveal a clonal B-cell population in most cases [16, 31, 32]. The finding of monotypic lymphoid cells on immunohistochemical analysis confirms the diagnosis of lymphoma. Localised AL amyloid differs from its systemic counterpart by the morphological appearance of the amyloid, and presence of clonal plasma cells and giant cells. It has been proposed that the pathogenesis of localised AL amyloidosis may differ from that of the systemic type, as suggested by the fact that in localised amyloidosis κ light chains are more frequent than the λ form, in contrast to the systemic form, where λ chains constitute the overwhelming majority of cases. It is suggested that oligomeric assemblies of the produced immunoglobulin light chain are toxic to plasma cells [33]. Light chains that compose amyloid deposits are the same as those expressed by the lymphoma cells. Such lymphomas are usually indolent and mildly symptomatic.

Sjögren's disease was found to be associated with pulmonary amyloidosisis and lymphoproliferative disorders. It manifests with multiple pulmonary large bullae, multiple nodules, parenchymal opacity and bronchiectasis [34, 35].

Histologically, the nodules are well circumscribed and are composed of homogeneous, densely eosinophilic material. Small aggregates of lymphocytes and plasma cells are usually found within or adjacent to the nodules. If amyloid is suspected, a Congo red stain should be performed and amyloid typing is needed. Interestingly, the light chains in nodular pulmonary amyloidosis are more frequently of the κ than the λ type, with a ratio of 3:1, in contrast to the λ predominance noted in most cases of systemic AL amyloidosis [16]. Some reports showed that serum amyloid A and transthyretin may be detected [20, 21, 36]. Differential diagnoses of nodular pulmonary amyloidosis include pulmonary hyalinising granuloma and amyloid-like nodules, particularly in light-chain deposition disease [37].

In a recent series, the outcome of 47 patients with pulmonary nodular AL amyloidosis was reported. Median (range) age was 65.5 (36–80) years and 13 were male. In nine (19%) cases, a serum or urine monoclonal protein was detected and 10 (21%) had an abnormal free light chain κ/λ ratio. A MALT cell lymphoma was also diagnosed in two patients. A surgical intervention was required in four cases. Only four (8%) cases were treated with chemotherapy: two with symptomatic pulmonary and two with lymph node amyloid deposits, with stabilisation of symptoms but no major improvement. In addition, 11 (23%) other patients were given chemotherapy for progression of underlying haematological disorders and not specifically for amyloid progression, with no substantial effect on the local amyloid deposits [26].

At our centre, between 2004 and 2016, we followed 49 patients with pulmonary nodular AL amyloidosis. Median (range) age was 69 (42–84) years and 60% were male. In 11 (22%) cases a serum or urine monoclonal protein was detected and 13 patients had an abnormal free light chain ratio. Sjögren's disease was diagnosed in three (6%) patients and a MALT cell lymphoma was also diagnosed in two patients. A surgical intervention was required in two cases. Systemic chemotherapy was performed due to progression of the primary lesion and association with systemic AL amyloidosis, each in one patient.

In general, nodular amyloidosis is treated satisfactorily by conservative excision, and the long-term prognosis is excellent.

Diffuse alveolar-septal amyloidosis

Diffuse alveolar-septal amyloidosis, also known as diffuse parenchymal amyloidosis, is characterised by the presence of amyloid deposits in the alveolar septa and vessel walls. As a rule, it is a manifestation of

systemic amyloidosis, but unusual cases of diffuse alveolar-septal amyloidosis with no evidence of a systemic disease have been described [29, 36, 38]. It is usually associated with systemic AL amyloidosis, but cases of diffuse alveolar-septal amyloidosis that are caused by systemic AA, systemic ATTRwt and systemic hereditary ATTR amyloidosis have been reported [28, 29, 38].

Because pulmonary impairment rarely dominates the clinical picture, pathologists most often encounter diffuse alveolar-septal amyloidosis as a *post mortem* finding. *Post mortem* series have confirmed that diffuse parenchymal amyloid is common in systemic AL amyloidosis. In an autopsy series, pulmonary involvement was found in 30% of 223 cases of patients with amyloidosis, including 14% with ATTRwt cardiac amyloidosis, 10% with AL amyloidosis and 4% with multiple myeloma [39]. In the series reported by BROWNING *et al.* [40], lung involvement was present at histological examination of *post mortem* tissue specimens in 18 (90%) out of 20 patients with AL amyloidosis and in eight (33%) out of 24 patients with AA. In a recent report from the Mayo Clinic [41], the authors reviewed the demographic and clinical features of 76 patients with autopsy-proven pulmonary amyloidosis. The diagnosis of AL amyloidosis was the most frequent and nearly all were diagnosed *ante mortem*; however, ATTR was mostly diagnosed at autopsy. In this series, alveolar septal involvement was seen in 59 patients (78%; AL n=44, ATTRwt n=11, ATTRm (mutated transthyretin) n=3 and apolipoprotein A-IV n=1). An *ante mortem* diagnosis of pulmonary AL amyloidosis was rendered only in one case. Interestingly, the authors concluded that the most common cause of death was cardiac amyloidosis [41]. Upon autopsy, the lungs are rubbery and their cut sections have a uniform spongelike appearance. Typically, all lobes are involved. The visceral pleura may be affected and pleural effusion is common. Diffuse alveolar septal amyloidosis manifests with widespread amyloid deposition involving the small vessels and the interstitium, with reticular opacities, interlobular septal thickening, micronodules and, less frequently, ground-glass opacification, traction bronchiectasias and honeycombing at high-resolution computed tomography (CT) [42] (figure 1). Diffuse amyloidosis is sometimes accompanied by mediastinal lymphadenopathy [28]. However, interstitial opacities may be subtle even in patients with overt clinical manifestations [43–45]. Factors that influence the pattern of amyloid deposition in amyloidosis remain unclear. However, in patients with systemic amyloidosis, pulmonary involvement is commonly demonstrable histopathologically at autopsy, but generally not diagnosed clinically [45]. Another autopsy study reported involvement of the lung parenchyma and vasculature in 11 out of 12 patients with AL, of whom only four were symptomatic, including one patient who died of pulmonary amyloidosis [46]. The lesions are typically hypocellular, but scant plasma cells may be present. Giant cells are not usually seen with diffuse alveolar-septal amyloidosis.

Lung involvement in light-chain deposition disease may mimic either diffuse alveolar-septal amyloidosis or nodular pulmonary amyloidosis [47]. Similar to systemic AL amyloidosis, light-chain deposition disease is a monoclonal plasma cell proliferative disorder. The diffuse form is histologically indistinguishable from diffuse alveolar-septal amyloidosis. However, nonamyloid light-chain deposits are Congo red-negative. Furthermore, electron microscopy reveals a granular material instead of the typical fibrils seen in amyloidosis. Light-chain deposition disease produces κ light chains as a rule, whereas λ light chains are more common in systemic AL amyloidosis and diffuse alveolar-septal amyloidosis [48, 49].
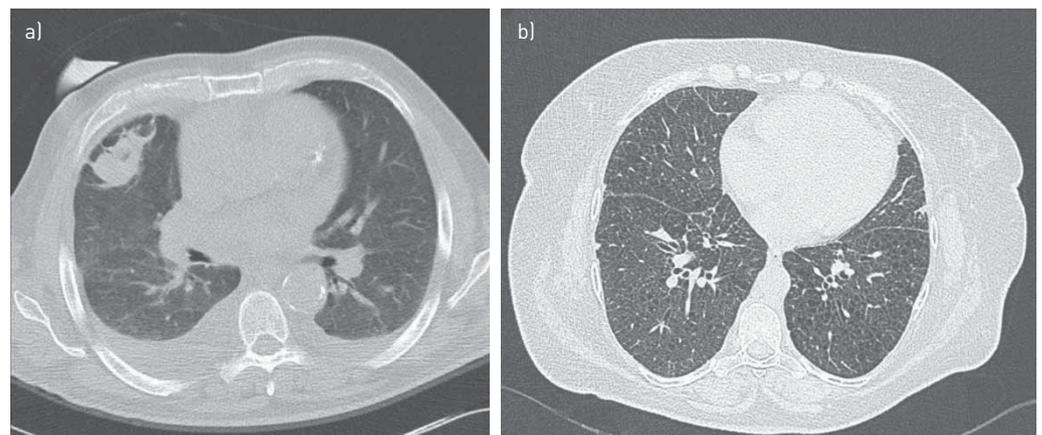

FIGURE 1 Radiology assessment of pulmonary amyloidosis. a) Computed tomography (CT) scan of the chest of a patient with nodular pulmonary amyloidosis; b) diffuse interstitial pulmonary amyloidosis in a patient with light-chain amyloidosis: high-resolution CT of the chest shows diffuse subpleural septal thickening.

Diffuse pulmonary amyloidosis has a remarkably different, more severe clinical presentation. The deposits involve the interstitium and affect gas exchange. Patients present with a progressive interstitial lung disease with dyspnoea (not explained by heart involvement) and an infiltrative imaging pattern. The pulmonary origin of the dyspnoea may be determined only after cardiac failure (from either congestive or restrictive cardiomyopathy) has been definitely excluded (with right heart catheterisation, if necessary). Recognition of pulmonary amyloidosis *ante mortem* might be facilitated by novel imaging techniques such as positron emission tomography using radiolabelled florbetapir [50]. This is reflected by lung function tests showing a restrictive pattern with reduced diffusion capacity of carbon monoxide (CO) and hypoxaemia upon exertion. These alterations are not commonly found in micronodular parenchymal amyloidosis; however, in patients with extensive involvement, micronodules and alveolar septal deposits may coexist. In addition, cysts and calcifications can be present [51].

Vascular deposits are common, but rarely clinically relevant, although they can give rise to pulmonary hypertension [45, 52, 53]. In patients with AL amyloidosis, the most common aetiologies of pulmonary hypertension are left-sided restrictive cardiomyopathy from amyloid deposition (group II pulmonary hypertension) or diffuse lung disease (group III pulmonary hypertension) [54, 55]. Pulmonary arterial hypertension (group I hypertension) is a rare but reported complication of primary amyloidosis [54, 55]. Pathologically, this is characterised by arterial deposits in the media. Pulmonary hypertension caused by lung involvement should be ruled out in patients without relevant cardiac amyloidosis and decreased CO diffusion. Pulmonary hypertension can occur in systemic AL amyloidosis and, less frequently, in AA amyloidosis secondary to familial Mediterranean fever [55, 56].

Rarely, the involvement of blood vessels can cause arterial dissection with bronchial bleeding [57], pulmonary haematomas or arteriovenous fistulas [58].

Interstitial amyloidosis occasionally occurs as a consequence of lung infiltration of B-cell malignancies [39, 45, 59] producing an amyloidogenic monoclonal protein, as well as in rare cases of lung metastases of medullary carcinoma of the thyroid [58–60]. In these cases, amyloid deposition is responsible for most of the infiltrative pattern on chest radiographs.

Diffuse alveolar-septal amyloidosis is treated according to the underlying systemic amyloidosis. In AL amyloidosis, reducing the concentration of the circulating free light chain rapidly and profoundly translates in the improvement of organ dysfunction and prolonged survival [61, 62]. Current treatment approaches derive from chemotherapy schemes developed for multiple myeloma. However, patients with AL amyloidosis are more fragile than multiple myeloma patients and are at a particularly high risk of death in the first few months following treatment initiation [63, 64]. Thus, treatment of AL amyloidosis should be risk-adapted and based on attenuated chemotherapy regimens and with a very close monitoring of treatment tolerability, particularly in the crucial months following diagnosis. Frequent assessment of the efficacy of chemotherapy is vital. Current criteria for haematological, cardiac and renal responses based on difference between involved and uninvolved free light chains, N-terminal pro-brain natriuretic peptide and proteinuria have been validated based on patient outcomes and should be used for individual patient management [62, 65]. The presence of lung amyloidosis could limit the treatment strategies; in particular, patients with CO diffusion capacity <50% cannot be considered for autologous stem cell transplant [66]. To date, there are no specific data concerning the impact of treatment of systemic AL amyloidosis on pulmonary involvement. Lung transplantation for isolated pulmonary amyloidosis has been reported [67].

Tracheobronchial amyloidosis

Tracheobronchial amyloidosis, most often presenting as multifocal submucosal plaques, is an organ-limited type of amyloidosis, which is usually not associated with detectable systemic lymphoplasmacytic clonal proliferation [28, 29, 44, 47, 59, 68–72]. The association with multiple myeloma is extremely rare [73]. Most cases represent localised AL amyloidosis and are restricted to this site. The pulmonary parenchyma is typically not involved, but colocalisation of laryngeal and tracheal amyloidosis has been described [74, 75]. In some cases of laryngotracheal involvement, subglottic amyloidosis may result in severe dyspnoea with fixed airflow obstruction at spirometry [76]. The mean age of patients with tracheobronchial amyloidosis is 50–60 years, with no sex predilection. It is usually symptomatic because of stenosis resulting from the amyloid deposits in the trachea and large bronchi. Patients present with cough and haemoptysis, which may occasionally be abundant. As is often the case in patients with subglottic stenosis of any origin, dyspnoea may for a long time be falsely diagnosed as asthma [77]. Narrowing of airways can cause wheezing, distal atelectasis, recurrent pneumonia or lobar collapse, and solitary nodules may be mistaken for endobronchial neoplasia [78, 79]. Lobar or segmental atelectasis found on imaging results from bronchial stenoses. Tracheal and bronchial wall thickening with possible calcification is observed at CT scan [76, 80]; calcifications usually spare the posterior tracheal wall [76]. On pulmonary

function tests, patients with proximal airway disease have decreased airflows, whereas patients with distal airway disease have normal airflows.

Tracheobronchial endoscopy usually shows irregular whitish deposits, most often diffuse, narrowing the airway lumen more or less completely (multifocal submucosal plaques). Three patterns of involvement have been described: proximal, mid- and distal airway disease [76]. Amyloid deposits are diffuse and typically involve the posterior wall of the trachea. The lesions are fragile and may bleed after biopsy. The deposits are localised to the submucosa and blood vessels, and are often associated with plasma cells and giant cells [29]. Squamous cell metaplasia may affect the epithelium and could be confused with carcinoma [81].

The management of tracheobronchial amyloidosis is largely dependent upon symptoms; there is no proven drug therapy for tracheobronchial amyloidosis, although systemic chemotherapy has been tried in patients with progressive disease [76]. Proximal and severe mid-airway disease can lead to airway compromise, which is usually treated with laser or forceps debridement or external beam radiation, which can sometimes suppress the responsible clonal B-cells within the tissue [76, 82, 83]. Tracheobronchial involvement may cause respiratory insufficiency and may favour infections that can be life threatening [76, 84].

Amyloidosis of the pleura

Pleural effusion is common in systemic amyloidosis [85–88]. Although most often transudative [89], exudative effusion is reported in one-third of cases. Involvement of the pleura is associated with effusions refractory to maximal diuretic therapy and thoracentesis, possibly because of impairment of resorption of pleural fluids [89]. Percutaneous or thoracoscopic pleural biopsy may thus be considered as a diagnostic procedure in patients with suspected amyloidosis and pleural effusion.

Conclusions

Amyloidosis of the lower respiratory tract is rare, but may represent a significant clinical problem in either systemic or organ-limited amyloidosis. In particular, in systemic AL amyloidosis, pulmonary interstitial involvement associated with cardiac amyloidosis can contribute to cardiopulmonary failure or even be the major problem in rare cases. Tracheobronchial involvement with resultant stenosis is the main symptomatic presentation in organ-limited amyloidosis. However, in the majority of patients, pulmonary amyloidosis (in particular if nodular) is an incidental finding of little if any clinical consequence. In any case, each patient requires complete assessment and unequivocal amyloid typing to determine their optimal treatment. Therapy, either local or systemic, is usually effective, although in few patients the control of the amyloid process may be problematic. Encouragingly, several drugs are now in the pipeline, which aim to stabilise the amyloid precursor proteins, interfere with amyloid fibrillogenesis and accelerate the clearance of tissue amyloid deposits, possibly benefitting patients with pulmonary amyloidosis.

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