Amyloidosis and the Lungs and Airways

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Summary

Amyloidosis can both complicate long-standing respiratory conditions and be deposited within the respiratory system itself. In localised amyloidosis management generally involves resection of symptomatic deposits. In acquired systemic amyloidosis treatment is controlling the underlying condition.

Introduction

Amyloidosis is due to the deposition of abnormal insoluble fibrillar plasma proteins within the extracellular space resulting in the disruption of tissue structure and organ function. It may be acquired or inherited and at least 30 proteins can form amyloid fibrils(1) (Table 1). There are essentially three circumstances in which amyloid deposition occurs. Firstly, with sustained abnormally high abundance of normal proteins, such as serum amyloid A protein (SAA) in chronic inflammation, or Beta-2-microglobulin in chronic renal failure. Secondly, when there is normal abundance of an inherently amyloidogenic protein over a prolonged period, such as transthyretin. Finally, the presence of an abnormal protein which is amyloidogenic, such as

monoclonal immunoglobulin light chains in AL amyloidosis or genetic variants of transthyretin, apolipoprotein AI and fibrinogen Aα chain.

All amyloid fibrils possess the ability to bind molecules of the dye Congo resulting in the pathognomonic apple green birefringence when viewed under cross polarised light. Amyloid deposits always contain the normal plasma glycoprotein, serum amyloid P (SAP) as a non-fibrillar constituent. The universal presence of SAP in amyloid forms the basis for diagnostic scintigraphic imaging of amyloid with radiolabelled SAP(2).

The phenotypes associated with amyloid deposition are diverse ranging from an asymptomatic small localised deposit to a systemic, rapidly lethal multisystem disease(3). Amyloid deposits are constantly turned over and clinical progression reflects when fibrillar deposition is greater than clearance(4). Amyloid deposits can therefore regress if this balance is tipped and current available therapies focus on halting the production of the amyloidogenic protein.

Diagnosis of Amyloidosis

Amyloidosis is a heterogenous disease presenting to a variety of different medical specialties including the respiratory physician. Chronic pulmonary conditions can give rise to systemic amyloidosis, most commonly of AA type, due to prolonged inflammation. Alternatively, patients may present with pulmonary amyloidosis, either localised to the respiratory tract or as part of a systemic process(5). Lastly pulmonary complications may also arise from treatment, especially in the context of AL amyloidosis.

The diagnostic gold-standard is by histological confirmation through Congo red staining(6, 7) (Figure 1). Alternative stains such as Thioflavin T or S can be used but generally reserved for the research setting. Biopsy of any organ can be hazardous in amyloidosis and there are reports of fatal lung haemorrhage following transbronchial biopsy due to amyloid infiltration into pulmonary vasculature(8). Haemorrhage is due to the increased fragility of involved blood vessels, reduced elasticity of amyloidotic tissues, and, occasionally in AL type due to an acquired factor IX or X deficiency(9, 10, 11). Alternatively, fine needle aspiration has been used successfully in the respiratory tract(12, 13, 14). Immunohistochemical (IHC) stains are then used determine the fibril protein type(5, 15) or with laser capture tandem mass spectrometry(16). There are advantages and disadvantages to each method. Generally, IHC is relatively inexpensive and useful in dual amyloid pathology but reliant upon expertise in interpreting results and subject to false positive rates especially with some commercial antibodies. In practice, type-determination of amyloid by IHC should be performed in specialist laboratories(17). In contrast, MS techniques are generally more sensitive but require a high level of technical expertise to perform and interpret. If a genetic variant is suspected more detailed analyses examining for specific mutations should be performed

Following histological confirmation, the extent of deposition in the respiratory tract needs to be ascertained although this can be challenging. Plain radiography can be helpful but is generally normal. Computed tomography (CT) scanning can further define interstitial disease. More commonly, pulmonary nodular amyloidosis, is characterised on CT scan by a variable number of nodules, in a peripheral or bilateral

subpleural location, with well-defined contours, variable size, slow growth, and occasionally cavitation that can result in the formation of thin-walled, cystic-like lesions (18). A more uncommon presentation is diffuse amyloid infiltration between alveolar septum and vessel wall which can manifest on CT as well-defined micronodules (2-4 mm), reticulation, thickening of the interlobular septa and peribronchovascular interstitium, ground-glass opacity, reticulonodular opacities or fine linear subpleural opacity that may converge and consolidate(19). Positron emission tomography (CT-PET) can better define the metabolic activity of a solid lesion, differentiating amyloid from more typical intrathoracic malignancies(20, 21). Magnetic resonance imaging (MRI) and bronchoscopy may be useful alongside comprehensive pulmonary function tests (PFTs). PFTs are an important objective tool to formally establish the severity of clinically relevant disease and are useful in guiding therapeutic decisions(22, 23). Evidence of systemic disease should be sought clinically and by performing haematological and biochemical profiles including serum free light chain assays, immunofixation of serum and urine and bone marrow examination to detect a potential subtle monoclonal disorder causing AL amyloidosis(24, 25, 26, 27).

SAP scintigraphy is useful in visualising amyloid in solid organs; localisation to the lungs is poor and of limited use in pulmonary amyloidosis(2). Cardiac amyloidosis is best evaluated by a combination of echocardiography, ECG and cardiac magnetic resonance imaging (CMR). Amyloid causes diastolic dysfunction with preserved contractility until a very late stage(28). The ECG may show small voltages, pathological ‘Q’ waves (pseudo-infarct pattern) in the anterior chest leads and conduction abnormalities in advanced disease. CMR is extremely useful in identifying

cardiac amyloid. Typical appearances are of homogenous late gadolinium enhancement(29). 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) scintigraphy is a specific test for ATTR amyloid although only if there is no evidence of an underlying clonal disorder(30, 31).

Systemic AA amyloidosis

Systemic AA amyloidosis is a potential complication of any disorder associated with a sustained acute phase response (Table 2). The prevalence of AA amyloid deposition in patients with chronic inflammatory diseases is between 3.6 and 5.8%, though a smaller proportion of patients have clinically significant amyloidosis(32, 33, 34). The amyloid fibrils are derived from the circulating acute phase reactant, SAA(35). SAA is an apolipoprotein of high density lipoprotein (HDL), which is synthesised by hepatocytes under the regulation of cytokines including IL-1, IL-6 and TNF-α(36). Normally the circulating concentration of SAA is around 1mg/l, but can rise by more than a thousand-fold in the presence of inflammation.

Median age at presentation is 48 and median latency between presentation with a chronic inflammatory disorder and clinically significant amyloidosis is almost two decades(37).

Bronchiectasis is the most common respiratory disease underlying AA amyloidosis in the UK accounting for 5% of cases. Patients primary immune deficiency are at higher risk and should be closely monitored (38).

Lung neoplasia including Castleman's tumours, lymphoma and adenocarcinoma account for 3%. Castleman's disease(39) is a rare B cell lymphoproliferative disorder often associated with marked constitutional symptoms. Acquired systemic amyloidosis is a recognized rare complication and is usually of systemic AA type occurring as a result of the persistent acute phase response(40, 41, 42, 43). In Castleman's disease there is production of IL-6 by the tumour and anti-IL-6 therapies can be highly effective(42, 43, 44, 45, 46, 47).

Other purely respiratory causes of AA amyloidosis are now fairly rare in the UK although tuberculosis remains in the developing world(48, 49, 50). Other rare associations include cystic fibrosis(51, 52), sarcoidosis(53) and Kartagener's syndrome(54).

AA amyloidosis usually presents with proteinuria, nephrotic syndrome and progressive renal failure(55). Splenic involvement is almost universal but often asymptomatic. Hepatic involvement and autonomic neuropathy are seen in advanced disease. Cardiac amyloidosis is extremely rare. Respiratory tract involvement has not been a clinical feature.

The most effective form of basic screening regular urinalysis in high risk patients as > 95% of patients with AA amyloidosis will have significant proteinuria. When the supply of fibril precursor protein is substantially reduced for sustained periods, AA amyloid deposits frequently regress and renal function can improve(37, 55, 56). If the acute

phase response continues unabated, progressive amyloid deposition often results in end stage renal failure.

Treatment depends on the underlying diagnosis and may include surgery for cytokine secreting tumours or localised bronchiectasis, long term antimicrobials and postural drainage for chronic infections, immunosuppression in inflammatory diseases such as sarcoidosis or even lung transplantation for bronchiectasis(57).

Almost 40% of patients with AA amyloidosis eventually require dialysis and have a median survival of 53 months. Mortality is higher in the first year and this has been attributed to ongoing nephrotic syndrome and increased risk of sepsis(58, 59). A minority of patients go on to receive renal transplants(59, 60, 61).

Systemic AL amyloidosis

AL amyloidosis is the commonest type of systemic amyloidosis accounting for more than 60% of cases(62) and can occur with any form of monoclonal B cell dyscrasia. The precursor proteins are monoclonal free light chains (FLC) consisting of the whole or part of the variable (V_L) domain(63).

A degree of amyloid deposition is seen in up to 15% of patients with myeloma, but more than 80%, who present with clinically significant AL amyloidosis have low levels of plasma cell marrow infiltration(64). AL amyloidosis usually presents over the age of 50 years, although it can occur in young adults(64). Clinical manifestations are extremely variable since almost any organ other than the brain can be directly involved(65).

Although specific clinical features can be strongly suggestive of AL amyloidosis (Table 3), multiple vital organ dysfunction is common and many patients present with non-specific symptoms such as malaise and weight loss. Current staging criteria are based on cardiac biomarkers, TroponinT and NTPro-BNP(66). Those with an NTProBNP >8500ng/l or a systolic blood pressure of <100mmHg have the worst prognosis (67). The outlook of untreated systemic AL amyloid is poor, with a 5-year survival of approximately 27% and a 10-year survival of 10%(64, 68). Most affected individuals eventually die of heart failure, uraemia or autonomic failure and 24 – 37% die within 6 months of diagnosis(69). This concerns systemic AL amyloidosis, in contrast to localised AL amyloidosis (discussed later) which is usually organ limited and overall has a better outcome.

Restrictive cardiomyopathy is the presenting feature in 30% of patients and ultimately the cause of death in half(70). Renal involvement is frequent in AL amyloidosis and presents in the same manner as renal AA amyloid(71). Gut involvement can cause motility disturbances, malabsorption, perforation, haemorrhage, or obstruction(72). Peripheral neuropathy occurs in 20% of cases and typically presents with a painful sensory polyneuropathy (64). Autonomic neuropathy may occur with or without a peripheral neuropathy(65).

A number of pulmonary conditions can underlie systemic AL amyloidosis. An isolated thoracic plasmacytoma can secrete enough monoclonal FLC into the circulation to produce systemic AL amyloid deposits(73) (Figure 2). Castleman's tumour is a rare cause of AL amyloidosis(74) as is Sjogren's syndrome (discussed later).

Although microscopic deposits of amyloid are universally present in the lungs, in most cases, dyspnoea is secondary to cardiac involvement(75, 76). Amyloid deposition in the small airways can result in a picture similar to pulmonary fibrosis. Lung function tests may show a restrictive pattern and reduced gas transfer(77). Radiographically the features can mimic interstitial infiltrative diseases(78). Plain films are normal or show a reticular pattern and CT shows interstitial infiltrates mimicking interstitial lung diseases. Fine interlobular thickening is often seen peripherally and/or sub-pleural. HRCT can show thin walled cystic spaces resembling emphysema and bullae that are secondary to amyloid deposition(79). The lesions are largely inert showing low or no metabolic activity on PET imaging(80). Chronic effusions secondary to pleural amyloid are often refractory to diuretics and require recurrent drainage or pleurodesis(81). Sleep-disordered breathing and apnoea can reflect cardiomyopathy, macroglossia, neuropathy and myopathy(82, 83).

The aim of treatment in AL amyloidosis is to suppress the underlying B-cell clone and production of the amyloidogenic FLC.(84). Despite effective therapy regression of amyloid is gradual and may not lead to measurable clinical improvement years(85, 86). Cardiac amyloidosis is particularly slow to regress, so patients with cardiac dysfunction may not live long enough to benefit from chemotherapy(87). However, many patients with AL amyloidosis do benefit and chemotherapy has led to improved survival (88). Treatment approaches are tailored to the individual based on guidelines established by the European Haematology Association and International Society for Amyloidosis (89, 90). Rigorous patient selection for high dose chemotherapy is essential as treatment

related mortality is extremely high in individuals with multiple organ involvement(91, 92, 93). Treatment response is monitored using the serum FLC assay. Reduction in FLC is associated with improved survival and organ response(94, 95, 96).

Immunomodulatory therapies such as Lenalidomide and Thalidomide, proteasome inhibitors such as Bortezomib and monoclonal antibody therapies such as Daratumumab form the backbone of therapy. Serious pulmonary side effects are rare but recognised with Bortezomib(97). Patients present with fever and asthma like symptoms which progress to respiratory failure and pulmonary infiltrates (98). There have also been reports of lung toxicity following Thalidomide(99) and Lenalidomide(100) with toxic granulomatous interstitial pulmonary disease which is steroid responsive. Thromboembolic risk is increased in some patients, especially with Thalidomide and Lenalidomide treatment and prophylactic anticoagulation should be considered(101)

Localised amyloidosis

First described by Lesser in 1877, this ranges from asymptomatic pulmonary nodules to diffuse parenchymal deposits(78, 102). Localised amyloid deposition results either from local production of fibril precursors(103, 104), or from properties inherent to the particular microenvironment which favour fibril formation of a widely distributed precursor protein(105). The vast majority of localised amyloid deposits are AL in type(102, 106, 107, 108) and symptomatic deposits occur most frequently in the eye(109), skin(110), respiratory(111, 112) or urogenital tracts(113, 114). They are often associated with extremely subtle focal monoclonal B cell proliferation confined to the affected site and surgical resection of these localised ‘amyloidomas’ can sometimes be

curative(114). Symptomatic localised amyloid deposits can rarely be manifestations of systemic disease but patients should always be fully investigated to exclude systemic amyloidosis(15).

The paucity of controlled clinical trials means that management decisions have to be made on an individual basis. Generally systemic chemotherapy is for systemic AL amyloidosis and local intervention, according to symptoms, for its localised forms.

Laryngeal amyloidosis

The larynx is the most frequent site of localised amyloidosis affecting the head and neck(115, 116). It represents 0.5-1% of benign laryngeal disease. Its incidence increases with age but can affect young adults or children(117) . The amyloid deposits commonly occur in the ventricles followed by the subglottis, the aryepiglottic folds and the true vocal cords(108). Presentation is usually with hoarseness, a sensation of 'fullness', choking, dyspnoea and, rarely, stridor(118). The aetiology remains unclear and there is no reported association with alcohol, smoking, vocal abuse or infection(115). One proposed explanation for the predilection is production of light chains arising from mucosal associated lymphoid tissue(112, 119). Light chain restriction is predominantly lambda(113, 120).

The diagnosis is usually made following laryngoscopy and biopsy. MRI is preferred when evaluating the extent of infiltration(121). Systemic amyloidosis should be excluded including investigation for an underlying plasma cell dyscrasia(116, 122).

There are case reports of extramedullary plasmacytoma with amyloid deposition affecting the larynx(123).

Localised laryngeal amyloid is usually benign but can be progressive or recur. Fatal haemorrhage has been reported(124). Endoscopic surgical(125, 126) or carbon-dioxide laser excision(127, 128) is the treatment of choice aiming to preserve voice quality and maintain airway patency(129). Corticosteroids have no effect(130). There are reports of successful external beam radiation therapy(131). Disease can recur in up to 25% of cases with a median time to recurrence of 34.5 months but reassuringly a mortality of <1% (132)

Very rarely localised laryngeal amyloid deposits can be due a feature of hereditary systemic apolipoprotein AI amyloidosis (AApoAI). Four separate apolipoprotein variants have been reported to cause this(104, 133, 134, 135), due to variable penetrance a family history is often lacking. Apolipoprotein AI is a constituent of high density lipoprotein (HDL)(136). Wild type apolipoprotein AI is amyloidogenic and is present as traces of amyloid in aortic atherosclerotic plaques in 10-20% of autopsies(137). AApoAI deposits as small irregular floppy proliferations affecting the borders of the vocal folds.

Tracheobronchial amyloidosis

Tracheobronchial amyloidosis is uncommon although likely underreported. Amyloid usual deposits in the trachea and large bronchi, with occasional extension into segmental bronchi. It can present with single or multiple nodules, luminal stenosis or

obstruction(111, 138, 139). A literature review identified 67 cases, of which 57 were diffusely infiltrative (multifocal submucosal plaques) and the remainder were nodular or ‘tumour-like’(140). Mean age is 52 years(141) and women tend to present more commonly and younger (25 - 45 years) than men (50 - 70 years), with more extensive disease and faster progression(142).

Presenting symptoms include dyspnoea, persistent cough, wheeze, haemoptysis, chest tightness and hoarseness(143). Deposits may cause distal atelectasis, recurrent pneumonia or lobar collapse(144) and solitary nodules may be mistaken for neoplasia(145) although 70% of a series had normal radiography(146). Typically deposits have intermediate T1 weighted signal intensity on MRI and low T2 weighted signal intensity similar to skeletal muscle(121). Early phase FDG metabolic activity can be seen on PET-CT but delayed images show reduced activity differentiating it from malignancy(147). Diagnosis is often delayed and made following bronchoscopy and biopsy(148). Differentials include tracheobronchopathia osteoplastica(149, 150, 151) and relapsing polychondritis(152, 153). Overall survival of 31% to 43% is reported at 6 years(111).

Management is largely dependent upon symptoms. There is no proven drug therapy, systemic chemotherapy has been tried in patients with progressive disease(143) as has dimethylsulfoxide. The most common strategies reported in the series by Lu with 53 patients included Nd-YAG laser, argon plasma coagulation, cryotherapy, topical drug, clamping, resection, high-frequency electrotome cautery, stent implantation, and microwaves. Extensive airway involvement may require open resection(154).

Endobronchial brachytherapy has been reported in a handful of cases with encouraging early results(155). Management will always need to be tailored and multi-modal therapeutic strategies combining airway recanalization and radiotherapy can be considered(156).

Parenchymal Pulmonary Amyloidosis

Amyloid within the lung parenchymal tissue is the most frequently detected respiratory manifestation of amyloidosis(157). It can be divided radiographically into solitary/multiple nodules or a diffuse alveolar-septal pattern(158, 159), the latter is usually a manifestation of systemic amyloidosis, most commonly AL but also reported with TTR type(5).

Nodular pulmonary amyloidosis is almost always localised AL and is usually an incidental finding on chest radiography with an excellent prognosis. In theory CT-PET should be useful in distinguishing between amyloid nodules and malignancy but case reports suggest that CT-PET can give false positive results so must be confirmed by histological diagnosis. Amyloid nodules are usually peripheral and subpleural, occurring preferentially in the lower lobes. They may be bilateral and range in diameter from 0.4-15 cm. They grow slowly and may cavitate or calcify(157, 158, 160). Larger nodules can occasionally produce space occupying effects or pneumothorax but generally no treatment is required. Rarely pulmonary amyloid nodules have been reported to be transthyretin amyloid in type (139, 161). Pulmonary nodules associated with AA amyloidosis have been found in patients with rheumatoid arthritis(162), Crohn’s disease (163) and in intravenous drug abuse(164) and run a benign course.

Amyloidosis in Sjogren's Disease

This chronic organ-specific autoimmune disease is characterized by lymphocytic infiltration into the salivary and lacrimal glands with an estimated prevalence of 0.5%, predominantly affecting women in middle life(165). It is associated with a 44-fold increase in lymphoproliferative disorders and 5% of patients develop malignant lymphoma. This evolution from polyclonal lymphoproliferation to clonal disease, mucosa-associated lymphoid tissue (MALT) lymphoma, or high-grade lymphoma is associated with an increasing risk of AL. Sjogren's disease is associated with a wide spectrum of respiratory manifestations ranging from sicca, obstructive small airway disease to interstitial lung disease, pulmonary hypertension and pleural involvement(166, 167).

Pulmonary amyloidosis associated with Sjogrens disease is a rare but well recognised complication and is most often associated with localised nodular pulmonary amyloidosis(168). It can also affect the breast tissues(169) or result in systemic disease(170). In a series(171), 96.5% were women with a median age of 59 (29 – 79) at presentation The most common symptoms were cough and dyspnoea. Over 90% occurred in primary Sjogren's disease and lymphoma was associated with 9% of cases. The diagnosis of pulmonary amyloidosis was made a median of 7 years (0 - 30) post initial symptoms. Amyloidosis associated with Sjogren's is predominantly AL however there have been a few isolated case reports of diffuse septal AA amyloidosis without evidence of amyloid deposition elsewhere(172, 173).

Amyloid Lymphadenopathy

Infiltration of lymphoid tissue by amyloidosis can result in massive lymphadenopathy (140). Sjogren's syndrome complicated by lymphoma is a recognised cause(140, 174). The majority of patients have a detectable circulating monoclonal immunoglobulin typically associated with very low grade lymphoplasmacytic lymphoma or Waldenstrom's Macroglobulinaemia(175). Initial investigations can be suspicious of lung cancer or granulomatous diseases and false positive PET findings have been described(176). CT imaging of amyloid lymphadenopathy has demonstrated considerable variety; calcification is not uncommon and low density areas within lymph nodes are described(159, 177). The diagnosis is often incidental following biopsy, and should prompt the search for an underlying B cell dyscrasia.

Disease progression is slow and calcification well recognised(159, 178). Amyloid adenopathy can occasionally cause tracheal compression and superior vena caval obstruction. Treatment centres on managing the underlying lymphoproliferative disease but surgical resection may become necessary.

Pleural Amyloidosis

Pleural involvement is commonly reported in systemic amyloidosis(179, 180) and can present with pleural effusion and pleural thickening (181). Diagnosis can be made via a video assisted thorascopic pleural biopsy (VATS). Unlike nodular pulmonary amyloidosis or tracheobronchial amyloidosis, pleural disease generally represents systemic disease such as AL amyloid or myeloma (182, 183)

Conclusion

Systemic amyloid can complicate long standing respiratory conditions or cause respiratory complications either directly or iatrogenically. Localised amyloid deposits can affect any part of the respiratory tract and may be incidental or symptomatic. In the absence of clinical trials management of localised amyloid deposits is guided by case series and tailored on an individual basis.

Table 1 Classification of the commoner types of systemic amyloidosis in man

Type	Fibril protein precursor	Clinical syndrome
AA	Serum amyloid A protein	Reactive systemic amyloidosis associated with chronic inflammatory diseases
AL	Monoclonal immunoglobulin light chains	Systemic amyloidosis associated with monoclonal plasma cell dyscrasias
AH	Monoclonal immunoglobulin heavy chains	Systemic amyloidosis associated with monoclonal plasma cell dyscrasias
Aβ_2M	Normal plasma β_2-microglobulin	Periarticular and, occasionally, systemic amyloidosis associated with long-term dialysis
Aβ_2M	Variant β_2-microglobulin	Autosomal dominant hereditary systemic amyloidosis
ATTR	Normal plasma transthyretin	Wild type systemic TTR amyloidosis with prominent cardiac involvement
ATTR	Genetically variant transthyretin	Autosomal dominant systemic amyloidosis Familial amyloid polyneuropathy or cardiomyopathy
ACys	Genetically variant cystatin C	Hereditary cerebral haemorrhage with cerebral and systemic amyloidosis
AGel	Genetically variant gelsolin	Autosomal dominant systemic amyloidosis Predominant cranial nerve involvement with lattice corneal dystrophy
ALys	Genetically variant lysozyme	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent visceral involvement
AApoAI	Genetically variant apolipoprotein AI	Autosomal dominant systemic amyloidosis Predominantly non-neuropathic with prominent viscera involvement
AApoAII	Genetically variant apolipoprotein AII	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
AApoAIV	apolipoprotein AIV	Sporadic systemic amyloidosis with predominant cardiac and renal involvement
AApoCII	Genetically variant apolipoprotein CII	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
AApoCIII	Genetically variant apolipoprotein CIII	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
AFib	Genetically variant fibrinogen A alpha chain	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
ALect 2	Leukocyte chemotactic factor 2	Sporadic slowly progressive renal amyloid with nephrotic syndrome and liver involvement
ALys	Genetically variant lysozyme	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal and hepatic involvement

Table 2 Conditions with Respiratory Manifestations associated with systemic AA amyloidosis

Category	Disease
Chronic infections	Bronchiectasis Q fever Subacute bacterial endocarditis Tuberculosis
Other conditions predisposing to chronic infections	Cystic fibrosis Kartagener's syndrome Quadraplegia Sickle cell anaemia
Immunodeficiency states	Common variable immunodeficiency Cyclic neutropenia Hyperimmunoglobulin M syndrome Hypogammaglobulinaemia Sex linked agammaglobulinaemia HIV/AIDS
Neoplasia	Adenocarcinoma of the lung, Carcinoid tumour Castleman's disease Hodgkin's disease Mesothelioma
Inflammatory arthritis	Adult Still's disease Ankylosing spondylitis Rheumatoid arthritis
Systemic vasculitis	Behcet's disease Systemic lupus erythematosis
Other	SAPHO syndrome Sarcoidosis Sinus histiocytosis with massive lymphadenopathy

Table 3 Clinical features associated with systemic AL amyloidosis

Organ involvement	Clinical Manifestation
Soft tissue infiltration	Bruising – especially periorbital; Macroglossia; Muscle/joint pseudo hypertrophy
Renal	Proteinuria; Nephrotic syndrome; Hypertension very rarely
Cardiac	Restrictive cardiomyopathy; Arrhythmias; Congestive cardiac failure
Hepatic	Hepatomegaly; Liver failure very rarely
Peripheral nervous system	Carpal tunnel syndrome; Symmetrical sensorimotor neuropathy
Autonomic nervous system	Orthostatic hypotension; Impotence; Disturbed bowel motility; Impaired bladder emptying
Gastrointestinal	Weight loss; Blood loss; Disturbed bowel motility
Lymphoretiicular	Splenomegaly ; Lymphadenopathy
Adrenal axis	Hypoadrenalism (rare)

Figure 1

A. Bronchial biopsy showing characteristic histological appearance of amorphous amyloid deposits stained with Congo Red.

B. Same section viewed under cross polarized light demonstrating apple green birefringence.

Figure 2

A. A CXR demonstrating a mass in the left upper lobe, this was diagnosed as a plasmacytoma with associated AL amyloid deposition following a biopsy.

B. A posterior whole body scintigraphic image from the same patient obtained following intravenous injection of ^{123}I-human SAP showing abnormal uptake into the amyloid deposits within the plasmacytoma and deposition in the spleen.

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