AL amyloidosis

Majid Kazmi

Abstract

Amyloidosis is a rare group of disorders with protean manifestations characterized by tissue deposition of misfolded protein. Removal of such deposits is poor, resulting in progressive accumulation of amyloid deposits and disruption of organ function. Among patients with systemic amyloidosis, AL-type protein is more common than AA (secondary amyloidosis), which is caused by chronic infection or chronic inflammatory disease. Familial amyloidoses are rare (estimated incidence <1 per 100,000). They are autosomal dominant inherited diseases with manifestations of amyloid deposition developing in mid-life. The most common form results from mutations in transthyretin protein. This article focuses on AL amyloidosis, formerly known as primary amyloidosis, which most frequently affects the kidneys, heart, liver and peripheral nervous system. Fatigue and weight loss are common, but diagnosis is rarely made until symptoms are referable to a particular organ. Untreated, it is progressive and fatal within 2 years in about 80% of patients. The three-step approach to diagnosis and investigation involves establishing the diagnosis, assessing the extent of organ involvement and excluding plasma cell dyscrasia/lymphoma. Treatment aims to reduce production of amyloidogenic light chains and stabilize organ function. New drugs classes such as proteasome inhibitors (e.g. bortezomib) and immunomodulatory agents (e.g. pomalidomide) show promise in rapidly reducing light-chain burden and halting amyloid production. Current research focuses on reducing amyloid load by interfering with protein misfolding and interaction with serum amyloid P protein.

Keywords AL amyloid; amyloidosis; chemotherapy; SAP scan; stem cell transplantation

Key points

- Amyloidosis is a rare diagnosis
- AL amyloidosis is potentially treatable with drugs that prevent production of amyloidogenic light chains
- A systematic approach to diagnosis and assessment of organ involvement is required before appropriate treatment can be offered for AL amyloidosis

Introduction

Amyloidosis is a rare group of disorders with protean manifestations characterized by the tissue deposition of misfolded protein. The body's capacity to remove such deposits is poor, resulting in a progressive accumulation of amyloid deposits and disruption of organ function.

Awareness of amyloidosis has increased in recent years, but most diagnoses are still made at an advanced stage of disease. It is important to differentiate the different types of amyloidosis as their treatments are different; there are over 20 different types of amyloid in humans. Among patients with systemic amyloidosis, AL type is most common, followed by AA type; hereditary amyloidosis accounts for about 10% of cases.

AL amyloidosis

Systemic AL amyloidosis occurs where there is extracellular accumulation of amyloidogenic monoclonal immunoglobulin light chain fragments in association with the normal plasma protein serum amyloid P (SAP). AL amyloidosis most frequently affects the kidneys, heart, liver and peripheral nervous system. Untreated, it is progressive and fatal within 2 years in about 80% of patients. The age-adjusted incidence of AL amyloidosis in the USA is estimated to be 5.1–12.8 per million persons per year; 60% of patients are 50–70 years old at diagnosis, and only 10% are aged <50 years. There is an equal male:female incidence. AL amyloidosis can be associated with myeloma or other B cell malignancy, but in most cases the underlying plasma cell dyscrasia is subtle.

Clinical features

Fatigue and weight loss are common, but the diagnosis is rarely made until symptoms referable to a particular organ appear. The most common clinical features at diagnosis are listed in Table 1. It is important to recognize, however, that AL amyloidosis can affect almost any organ or tissue in the body other than the brain.

Diagnosis and investigation

The approach to diagnosis and investigation is a three-stage process. In the UK, it is recommended that all cases of amyloid are referred to, or at least discussed with, the National Amyloidosis Centre (www.ucl.ac.uk/medicine/amyloidosis/nac). The stages are as follows:

1. *Establish the diagnosis of AL amyloid* – amyloid deposits stained with Congo red produce red–green birefringence when viewed under cross-polarized light. Amyloid is usually diagnosed by biopsy of an affected organ, although less invasive alternatives can be considered (e.g. subcutaneous fat aspirate). Bone marrow involvement with amyloid is strongly suggestive of AL amyloid (Figures 1 and 2). Owing to poor sensitivity of immunohistochemical staining for light chains (60%), AL amyloidosis is often diagnosed after exclusion of AA and hereditary types by immunohistochemistry and genetic sequencing, respectively. In cases of doubt, amyloid fibril gene sequencing or mass spectrometry should be undertaken.
2. *Search for evidence for involvement by amyloid within other organs* (Table 2).
3. *Evaluation of plasma cell dyscrasia/lymphoma.*

It is important to exclude a diagnosis of myeloma or other lymphoid malignancy.

Majid Kazmi *FRCP FRCPath is a Consultant Haematologist at Guy's and ST Thomas' NHS Foundation Trust, UK.* *Competing interests: none declared.*

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Most common organ-specific manifestations of AL amyloid

Affected organ	Approximate incidence	Clinical features
Renal amyloid	33%	Proteinuria and nephrotic syndrome with or without renal insufficiency. Orthostatic hypotension
Cardiac involvement	20%	Reduced QRS complexes on electrocardiography Restrictive cardiomyopathy, orthostatic hypotension
Neurological involvement	20%	• Sensory most commonly symmetrical • Motor rare • Carpal tunnel syndrome • Autonomic peripheral neuropathy with gastrointestinal dysmotility, severe orthostatic hypotension, weight loss, sexual dysfunction, bladder dysfunction, abnormal sweating
Organ enlargement	25% 10%	Hepatomegaly Macroglossia
Haemostatic involvement	50% (Mumford et al. 2000[a])	Abnormal clotting screen Bleeding diathesis including peri-orbital purpura ('raccoon eyes')

[a] Mumford, A.D., O'Donnell, J., Gillmore, J.D., et al. Bleeding symptoms and coagulation abnormalities in 337 patients with AL amyloidosis. *Br. J. Haematol* 2000; **110**: 454–460.

Table 1

Prognostic factors

Patient survival has steadily improved from a median of 1–2 years in the 1980s to >5 years in recent series,[1] reflecting a combination of better supportive care and more successful treatment strategies. A poorer prognosis is associated with symptomatic cardiac disease, forming the basis of the Revised Mayo staging criteria.[2]

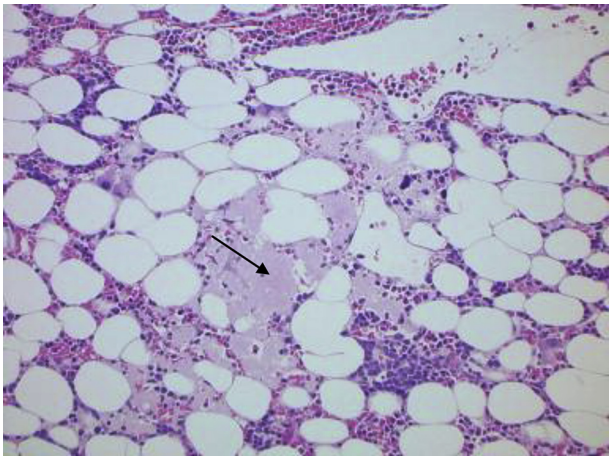

Figure 1 AL amyloid in the bone marrow (interstitial; arrowed).

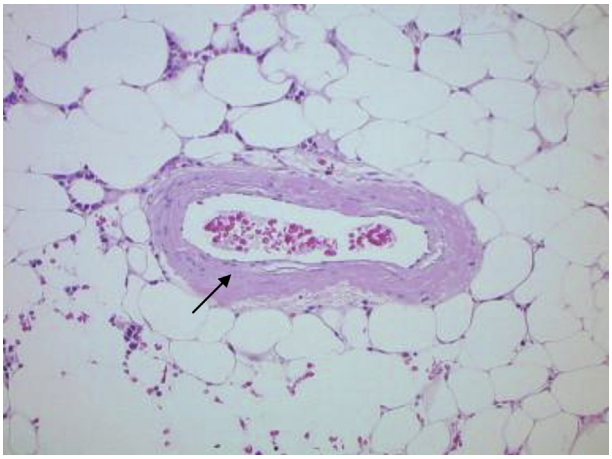

Figure 2 AL amyloid in the bone marrow (vessel wall; arrowed).

Treatment

Localized AL amyloid (non-vital organ)

The course of the disease is relatively benign in most patients. In some cases, local surgical intervention is appropriate.

Systemic AL amyloid including vital organ involvement

Treatment that specifically removes amyloid deposits are in early development, and therapy currently aims to suppress the production of clonal light chains, and thus slow or halt continuing amyloid deposition, along with measures supporting organ function.

Numerous case series have shown that patients who achieve complete or near-complete clonal responses have better outcomes in terms of both patient survival and improvement in amyloidotic organ dysfunction.[3]

Evaluation of organ involvement with AL amyloid

System involved	Tests
Generic	Full blood count, clotting screen, skeletal survey, chest X-ray, SAP scan[a]
Renal	Renal function tests, Quantification of proteinuria — 24-hour urine collection or protein/creatinine ratio calculation
Liver	Liver function tests
Cardiac	ECG/echocardiogram/NT-proBNP and cardiac troponin, cardiac MRI
Respiratory	Pulmonary function tests
Neurological	Nerve conduction studies and autonomic function tests

ECG, electrocardiography; MRI, magnetic resonance imaging; N-terminal pro b-type Natriuretic Peptide (NT-proBNP).

[a] SAP scintigraphy. This investigation is available only at the NHS National Amyloidosis Centre, allows diagnosis and quantification of deposits, and is useful in assessing the extent and distribution of organ involvement and evaluating the effects of treatment.

Table 2

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