

Systemic amyloidosis with cardiac involvement

Amyloidosis is a term used to describe a group of disorders consisting of abnormalities in and the accumulation of amyloid protein. This protein cannot be degraded and so collects in the tissues, interrupting both their structure and function. The disorder is progressive as amyloid increases and symptoms vary depending on the affected organs, which can be localised or systemic. We discuss diagnosis and management of amyloidosis with cardiac involvement and describe a case presenting in late life with rapid progression.

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Amyloidosis is a term used to describe a group of disorders arising due to abnormalities in and the accumulation of amyloid protein.¹ The affected protein misfolds, as a result of mutation or excess production, and forms β -pleated sheets that align perpendicularly, thus forming an insoluble amyloid fibril that resists enzymatic degradation and causes oxidative stress in affected organs.² Amyloid protein collects in the tissues and interrupts both the structure and function of these tissues. The disorder is progressive as the amyloid increases, and symptoms vary depending on the affected organs.

Types of amyloidosis

Classification of amyloidosis has historically been on a clinical basis and consisted of primary and secondary amyloidosis.³ Clinicians should first assess whether the patient has localised or systemic amyloidosis. Localised amyloidosis, confined to one

organ, generally has a good long-term prognosis.⁴

Distinguishing between the different forms of amyloidosis is clinically difficult (table 1).⁴ Amyloid light chain (AL) amyloidosis is a primary systemic amyloidosis of unknown cause. The incidence of AL amyloidosis is difficult to precisely

“About 20% of cases have predominately cardiac symptoms at diagnosis. Cardiac involvement is associated with a poor prognosis.”

define; however, extrapolation from US figures gives an age-adjusted incidence of approximately 600 new cases per year in the UK.⁸ In this form of amyloidosis, defective plasma cells produce amyloid immunoglobulin light-chains.²

Secondary, or reactive, amyloidosis arises from serum

amyloid-A protein associated with rheumatoid arthritis, chronic infection, and inflammatory bowel disease. Senile systemic amyloidosis affects organs such as the heart, brain, kidneys, and liver, and consists of amyloid transthyretin.

Hereditary amyloidosis is an autosomal dominant disease in which patients produce mutated transthyretin or, less frequently, apolipoprotein-1. Isolated atrial amyloidosis involves atrial natriuretic peptide and its incidence increases with age. Haemodialysis-related amyloidosis results from a long-term accumulation of β_2 -microglobulin (table 1).²

Presentation and symptoms

Data from patients evaluated at the UK National Centre for Amyloidosis show that 66% of patients were aged 50–70 years old at diagnosis, with an equal male-to-female ratio.⁹ Yet, international review papers frequently state that it is more common in men than in women

Type of amyloid fibril	Signs and symptoms	Diagnostic tests	Treatment	Median survival
Primary (AL)	Heart failure (22–34% of cases) Renal failure Proteinuria Hepatomegaly Autonomic dysfunction Peripheral neuropathy Enlarged tongue Purpura Neuropathy Carpal tunnel syndrome	Serum protein electrophoresis Urine protein electrophoresis Bone marrow biopsy tissue analysis showing plasma cell dyscrasia λ and κ -light chain antiserum staining	Chemotherapy (usually high-dose melphalan, then intermediate-dose melphalan, or dexamethasone) Autologous stem-cell transplantation Diuretics indicated for heart failure (angiotensin converting enzyme inhibitors need extreme caution, calcium channel antagonists, β -blockers and digoxin are contraindicated)	13 months 4 months if patient has heart failure at diagnosis
Hereditary (ATTR)	Heart failure Severe neuropathy Autonomic dysfunction Renal failure Blindness	Amyloid transthyretin antiserum staining Serum transthyretin isoelectric focusing Restriction fragment length polymorphism analysis	Liver transplantation (cardiac amyloidosis can progress after liver transplantation)	70 months
Hereditary (AApoA1)	Renal failure Heart failure	..	Cardiac transplantation	..
Senile systemic (ATTR)	Heart failure Can involve other organs Affects elderly men almost exclusively	Amyloid transthyretin antiserum staining	Supportive therapy for symptoms	75 months
Isolated atrial (AANF)	Affects atrium only	Atrial natriuretic factor antiserum staining	None required, may cause atrial fibrillation	..
Reactive (AA)	Renal failure Proteinuria Heart failure Hepatomegaly	Target organ biopsy sample Amyloid A antiserum staining	Treat underlying inflammatory process	24.5 months
Dialysis related	Arthralgia Arthropathy Skeletal cysts Fractures Carpal tunnel syndrome	Synovial and bone biopsy samples β 2-microglobulin antiserum staining Serum β 2-microglobulin concentration	Kidney transplantation	..

Table 1: Classification of subtypes of cardiac amyloidosis^{2,5-7}

Case history

A 72-year-old woman, with no past medical or family history of relevance was referred to our outpatients department with a 3-month history of palpitations and rash affecting her torso and limbs. Examination confirmed fast atrial fibrillation and purpuric rash affecting her chest and lower limbs (figure 1). The rash was pressure sensitive, with new areas of rash occurring, or established areas worsening, after application of even minimum pressure to the skin. A minor scratch soon became purpuric. Periorbital bruising was also present (figure 2). The patient was not anaemic; renal and liver function and a coagulation screen were normal.

Skin biopsy of the purpuric rash was requested and a congo-red stain was done. Amyloid deposits were seen in the subcutaneous fat (seen in 80% of cases⁷), epidermal layer, and blood vessels. Further immunohistochemical staining of the amyloid deposits revealed λ -light chains. A trephine bone-marrow biopsy sample was taken and key markers—CD138, κ -light chains and λ -light chains—were assessed and counted, which were all normal. Urine testing revealed λ -light chains and 24-hour urine collection showed high protein concentration (table 2). Serum immunoglobulin analysis was done for IgA, IgG, and IgM (table 2). No paraprotein was detected. We also tested concentrations of serum free κ -light chains and λ -light chains (table 2). All these tests are important prognostic indicators in amyloidosis. In a case series, 89% of patients with primary amyloidosis had light chains present in urine or serum protein immunofixation electrophoresis. The protein was primarily λ , with a κ : λ ratio of 1:2 (1:65 in our patient).² Echocardiography demonstrated good left ventricular function with an ejection fraction of 58%. However, the intraventricular septum and left ventricular posterior wall were thickened suggesting amyloid infiltration.

At this point we referred the patient to the National Amyloidosis Centre for review and further investigation, where she underwent serum amyloid-P scintigraphy. In this patient's case the scan revealed a small total body load of amyloid, present only in the spleen. However, this imaging technique is poor at identifying cardiac deposits. A diagnosis of AL type amyloidosis was made. The patient developed heart failure which was treated initially with high-dose intravenous furosemide. She was stabilised after several weeks on furosemide 80 mg twice daily, metolazone 2.5mg daily, and bisoprolol 2.5mg daily. Further dose increases of diuretics and the introduction of angiotensin converting enzyme inhibitors were prevented due to hypotension (blood pressure 80/60). The patient deteriorated rapidly and died from cardiac failure 3 months after diagnosis.

with a ratio of 3:2.^{2,7} About 20% of cases have predominately cardiac symptoms at diagnosis,⁹ and about 60% of patients will develop electrocardiographic or echocardiographic abnormalities.² Cardiac involvement is associated with a poor prognosis.¹⁰

A third of patients with amyloidosis have cutaneous presentations manifesting as purpura.⁹ Cutaneous purpura occur

because of amyloid infiltration of the capillaries and small vessel walls in the skin causing linear purpura typically seen after scratching and pinch purpura in areas under pressure. Periorbital purpura, known as the raccoon sign, is a typical clinical sign of amyloid disease and can be either spontaneous or provoked by rubbing the eyes, but may be mistaken for simple bruising. Periorbital purpura

and enlarged tongue are almost pathognomonic of amyloidosis.⁷

Doctors should consider amyloidosis in patients presenting with a combination of symptoms, such as fatigue, weight loss, easy bruising, rapid-onset breathlessness, peripheral oedema, sensory change (including carpal tunnel syndrome), postural hypotension, and unexplained renal disease.⁶ Patients with cardiac involvement predominantly present with heart failure due to restrictive myopathy, and atrial fibrillation is common.²

Diagnosis

Diagnosis requires a high index of suspicion and should be confirmed with tissue biopsy. Further investigations are then required to establish the type (table 1).⁹ Pathological investigations include immunohistochemical staining of tissue; histological and immunological diagnosis is obtained via routine electrophoresis and immunofixation. Congo red staining highlights the amyloid protein red with green birefringence when viewed under polarised light. This result is diagnostic of amyloidosis, but identifying the type of amyloid is clinically necessary to determine treatment options.⁴

The imaging modality of choice is serum amyloid-P scintigraphy since the glycoprotein amyloid-P is present in all forms of amyloidosis, accounting for 15% of the amyloid deposit.^{4,6} This imaging method uses a radioactive tracer to show the distribution and amount of amyloid within the body's organs and has 90% sensitivity.⁷ This scan determines the extent and amount of amyloid deposits and, in conjunction with the other tests, determines prognosis.

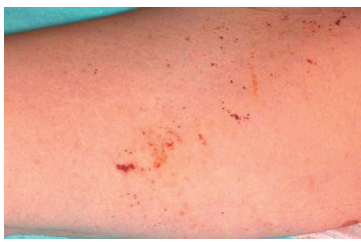


Figure 1: Purpuric rash



Figure 2: Periorbital bruising

Treatment of AL amyloidosis

Treatment of amyloidosis can be difficult and consists of both specific treatments for amyloidosis and symptomatic management.¹¹ The mainstay of symptomatic treatment in cardiac disease is diuretic therapy, whilst the mainstay of targeted therapy is chemotherapy and steroids. The decision to use treatments targeted at amyloidosis depends on the type and severity of the disease, and requires expert input.

Symptomatic treatment of cardiac amyloidosis is difficult because many treatments are contraindicated, for example, angiotensin converting enzyme inhibitors should be used with caution because of the risk of orthostatic hypotension.⁶ Agents with negative inotropy, such as β -blockers, should be avoided, as should calcium channel blockers, which can exacerbate diastolic dysfunction.⁶ Digoxin can bind to amyloid fibrils leading to digoxin

toxicity.² Pacemakers may be useful in patients meeting implantation criteria; they improve symptoms but do not improve survival.²

If our patient had presented earlier, treatment options could have included chemotherapy or autologous stem cell transplantation, or both. Survival benefits of chemotherapy are not good, and are limited to those without cardiac involvement.² High-dose melphalan and stem-cell transplantation has a clonal response rate of 76% (partial and complete response) and complete remission of 33%; the respective figures for intermediate-dose melphalan and stem-cell transplantation are 53% and 18%. The average survival is 7.8 years, but treatment-related mortality is fairly high at 12–13%.¹²

Melphalan and dexamethasone gives a clonal response of 67%, and 33% complete remission; treatment-related mortality is much lower at 4%, but survival is also reduced at 5.1 years. This regimen is used for patients whose disease is too advanced for stem-cell transplantation to be an option. High-dose dexamethasone gives clonal response of 53% and complete remission of 24%. Treatment related mortality is 7% and survival is 2.6 years only.

Thalidomide plus dexamethasone results in clonal response in 48% and complete response of 19%. This regimen is an option for those who cannot undergo stem-cell transplantation. It is not associated with death but 65% of patients have serious adverse events: survival is less than 3 years.¹²

A final treatment option is melphalan with prednisolone, but clonal response is 28% with rare instances of complete remission; treatment-related mortality is 0% and survival is a mere 1.5 years.¹² Vincristine cannot be used if the patient has peripheral neuropathy. Doxorubicin cannot be used for a long period, if at all because of its cardiotoxicity.⁷ Heart transplantation is not indicated because of disease recurrence, but in hereditary transthyretin amyloidosis, liver transplantation removes the source of amyloid and is curative.²

All cases should be referred to the UK National Amyloid Centre for assessment and advice. However, patients are usually managed locally by specialists of the main organ affected or those whose speciality precipitates secondary amyloidosis. Thus, a cardiologist may manage the patient with primary

	Result	Normal range
24-hour urine collection	0.26 g/l	0.00–0.15 g/l
Serum IgA	2.7 g/l	0.8–4.0 g/l
Serum IgG	10.9 g/l	6.0–16.0 g/l
Serum IgM	0.4 g/l	0.5–2.0 g/l
Serum κ -light chains	0.028 g/l	0.0033–0.0194 g/l
Serum λ -light chains	1.821 g/l	0.0057–0.0263 g/l
κ : λ ratio	0.02	0.26–1.65

Table 2: Results of our patient's blood tests

amyloidosis who presents with heart failure due to a restrictive cardiomyopathy. A rheumatologist may manage the condition in a patient with chronic rheumatoid arthritis who develops secondary amyloidosis.

The mean survival for patients with AL amyloidosis is 1–2 years,¹³ however, this is reduced with symptomatic or substantial echocardiogram evidence of cardiac disease.¹⁴ This reduced prognosis proved to be the case in our patient with death occurring 3 months after diagnosis. Amyloidosis requires vigilance and thorough investigation so that early diagnosis can be made, and expert input sought. Prognosis, however, remains poor in the majority of cases.

We have no conflict of interest. Written consent was obtained from the patient for publication of this case report and the accompanying images.

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