PRIMARY CARDIAC INVOLVEMENT OF 'AL' AMYLOIDOSIS

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INTRODUCTION

Since Rudolf Virchow first described amyloid in 1854, we have come to understand more about this peculiar and diverse disease entity collectively known as amyloidosis[1]. It is a rare condition, with an incidence of 8 per million per year[2]. Recommended classification depends on the type of insoluble fibrillar protein forming the amyloid deposits, thus there are between 18-20 different types of amyloidosis[3].

However, for practical purposes, amyloidosis can also be classified[4] clinically as:

- primary
- secondary
- hereditary
- age related (senile)

It can also be classified[5] into:

- systemic (including AL (immunoglobulin light chain) and AA (amyloid A) amyloidosis)
- localised (including those seen in Alzheimers disease and skin) forms

Diagnosing any of the myriad forms of amyloidosis is difficult at best due to its varied and non-specific presentations[2,5]. We report the difficulties in diagnosing AL amyloidosis (with primary cardiac involvement) in a patient with common symptoms and signs.

CASE REPORT

In June 2005, a 62-year-old woman was admitted from our outpatient clinic with signs of decompensated biventricular heart failure including dyspnoea on minimal exertion, ascites, hepatomegaly 5cm below the subcostal margin, jugular venous pressure of 7cm and gross bilateral pitting oedema up to the mid-thigh level. Review of her casenotes revealed symptoms which started from February 2004, when following an episode of abdominal pain she passed blood clots rectally for several days. She had a barium enema which was reported as normal and two flexible sigmoidoscopies which showed a stricture in the sigmoid colon. Biopsies taken showed normal epithelium and granulation tissue. These findings were thought to be due to ischaemic colitis and a repeat barium enema was arranged. However, by then the patient was completely asymptomatic and declined further investigations. She also noticed intermittent, self-limiting purpuric lesions affecting her head and neck. In the presence of normal coagulation studies, the lesions were not investigated further (figures 1 and 2).

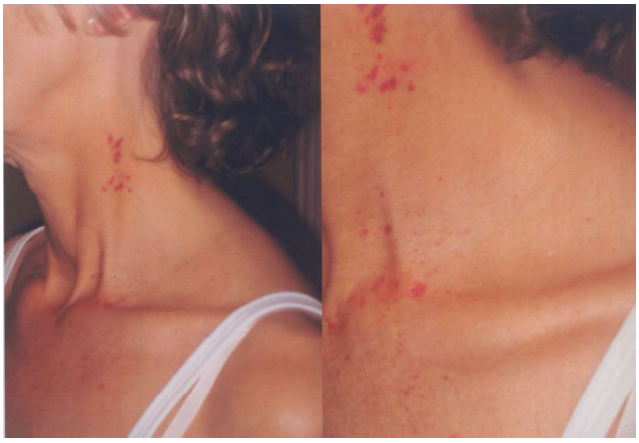

Figure 1 Lateral view of some of the purpuric lesions affecting the neck

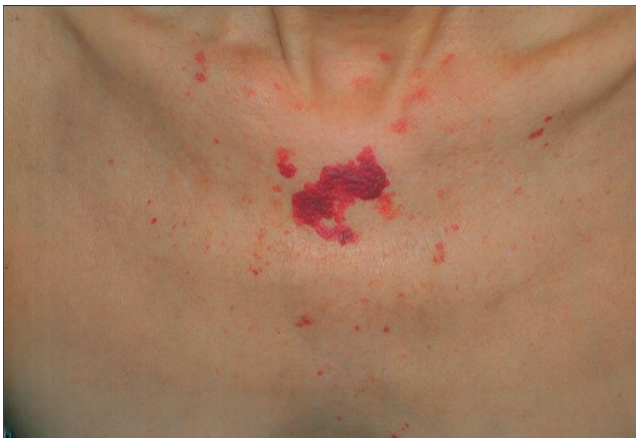

Figure 2 Anterior view of a large purpuric lesion affecting the sternal area

In January 2005, she had been admitted with pneumonia associated with purpuric rash and during her stay had a series of investigations including high resolution computerised tomography (HRCT), computerised tomography pulmonary angiography (CTPA), viral and comprehensive autoimmune screening, all of which were normal. She continued to experience progressively worsening dyspnoea on minimal exertion in the absence of any smoking history. Initial spirometry showed a FEV_1 of 48.7% predicted and peak expiratory flow rate (PEFR) monitoring showed significant variability with morning dipping. She was suspected to have late-onset bronchial asthma and commenced on regular inhalers. A full pulmonary function test (PFT) later showed a mixed obstructive and restrictive ventilatory defect (figures 3 and 4, table 1).

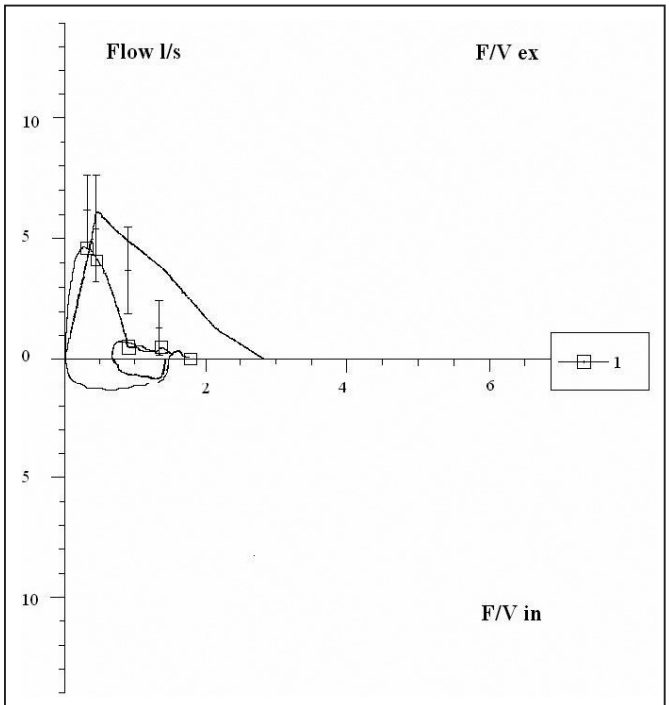

Figure 3 Flow-volume loop showing reduced maximal flow rate and volume with features of chronic obstruction

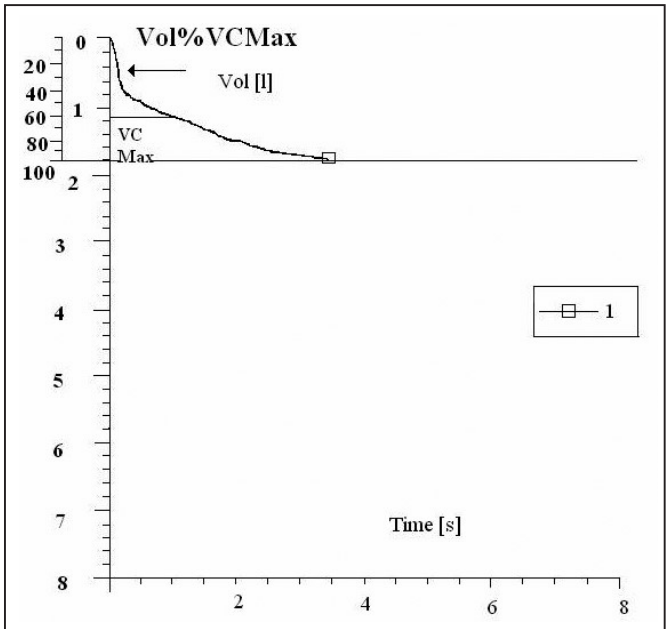

Figure 4 Volume versus time loop of the same patient

	Predicted	Best	% Predicted
RV-He ..... [1]	1.96	1.53	78.1
RV%TLC-He ..... [%]	39.70	43.40	109.3
TLC-He ..... [1]	5.10	3.53	69.3
FRC-He ..... [1]	2.76	2.02	73.2
FVC ..... [1]	2.83	1.79	63.1
FEV 1 ..... [1]	2.39	1.17	48.7
FEV 1 % FVC ..... [%]		65.21	
VC IN ..... [1]	2.95	1.83	62.2
VC EX ..... [1]	2.95	1.58	53.8
ERV ..... [1]	0.79	0.49	61.2
TLC SB ..... [mmol/min/kPa]	7.77	4.59	59.1
TLCOc SB ... [mmol/min/kPa]	7.77	4.58	59.0
KCOc ..... [mmol/min/kPa/l]	1.52	1.35	88.3
VA ..... [1]	4.95	3.40	68.8
Hb ..... [g/100ml]		13.50	

Table 1 Volumes and capacities following pulmonary function testing showing mixed obstructive and restrictive ventilatory defects

In March 2005 there was a further admission with pulmonary oedema, where she underwent extensive cardiac investigations including echocardiography and ventilation/perfusion (V/Q) scanning, which were normal, with an ejection fraction (EF) of 55-65%. She was reviewed again in May 2005 and arrangements were made to follow her up with repeat echocardiography, exercise tolerance testing and 24-hour Holter monitoring. However, her admission in June 2005 brought these plans forward. She was treated with intravenous frusemide in combination with oral metolazone, spironolactone and perindopril. Again, she was extensively investigated (table 2). The results were disproportionate with the clinical finding of severe congestive cardiac failure (CCF). Also interesting was the feature of abnormally 'bright' myocardium on echocardiography which was not reported in previous studies (figure 5).

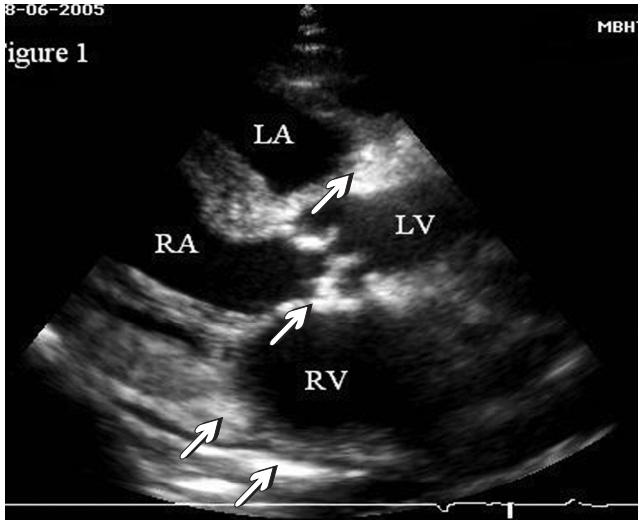

Figure 5 2-D 4 chamber view echocardiogram of the patient showing the abnormally diffuse bright myocardium indicated by the arrows

Important Findings of Inpatient Investigations	
24-Hour Tape	• Evidence of SA & AV node disease • 1st degree heart block throughout • Ventricular & atrial ectopic beats
Electrocardiography	• No significant abnormality • Rather low voltage
Repeat Echocardiography	• Abnormal right & left ventricular function • Thickening of all valves • Ejection fraction 50% • Abnormally bright myocardium • Restrictive pattern on Doppler
Coronary Angiography	• Minimal coronary atheroma, no obstruction
Liver Function & Coagulation Screen	• Normal, Albumin between 38-40 g/l
Urea & Electrolytes	• Sodium between 121-130 mmol/l • Potassium between 4.5-5.3 mmol/l • Urea 15 mmol/l, Creatinine 125 micromol/l
24-Hour Urine Collection	• Reduced creatinine clearance 28 ml/min • No significant protein loss

Table 2 Results of investigations following admission in June 2005

At this point she was referred for an endomyocardial biopsy and further investigations at a tertiary centre. The biopsy specimens showed characteristic bright green fluorescence (viewed under polarised light) after staining with Congo Red (Figures 6, 7 and 8). A bone marrow biopsy showed 21% abnormal plasma cells suggestive of myeloma. A skeletal survey done showed lytic lesions in both humeri and possibly the skull and spine. She was transferred to the National Amyloidosis Centre for more investigations including immuno-histochemical analysis (table 3). 123I-labelled

serum amyloid-P (SAP) scintigraphy showed amyloid load in spleen, intestines and kidneys. The diagnosis of AL amyloidosis with primary cardiac involvement in association with renal, gastrointestinal, skin and bone involvement was made. She was commenced on CTD (cyclophosphamide, thalidomide, dexamethasone) chemotherapy. Due to the significant risk of thromboembolism thalidomide was discontinued, and due to fluid retention dexamethasone was discontinued. Diuretic therapy with frusemide and bumetanide continued. Despite these efforts, the patient died two months later. A post mortem was not held.

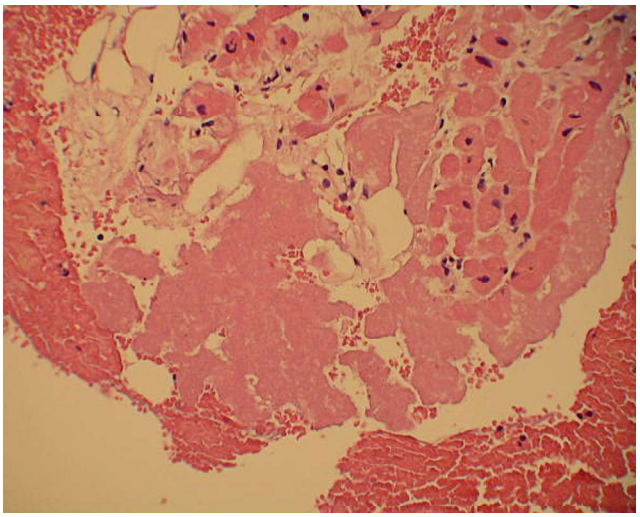

Figure 6 Cardiac biopsy H & E stain

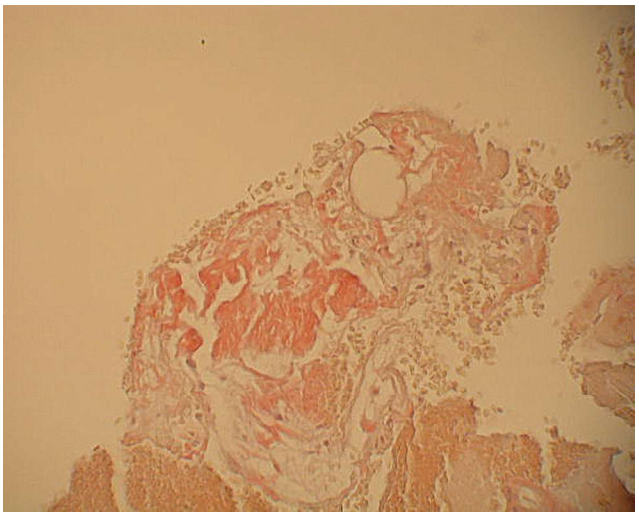

Figure 7 Cardiac biopsy Congo Red stain

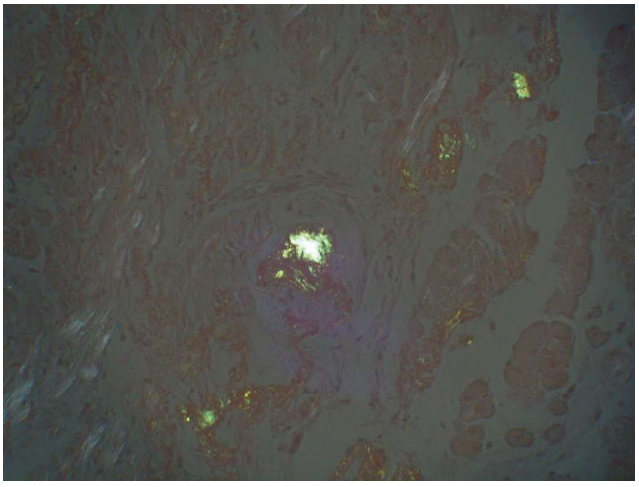

Figure 8 Viewed under polarised light

Findings of Serum and Urine Immuno-histochemical Analysis	
Serum κ light chains	• 2430 mg/l
Serum λ light chains	• 7.8 mg/l
κ: λ ratio	• 312
Serum immunoglobulins	• IgA reduced at 0.5 g/l • IgG reduced at 4.1 g/l • IgM reduced at 0.2 g/l
Urine electrophoresis	• Bence-Jones κ chains <20 mg/l

Table 3 Summary of results of serum and urine immuno-histochemical studies at the National Amyloidosis Centre

DISCUSSION

It is well known that the symptoms and signs of amyloidosis are frequently vague and non-specific ranging from fatigue, fluid retention and weight loss to those due to underlying organ involvement[2,5,6,7]. Therefore, in the absence of histological evidence, it is easy to misinterpret and misdiagnose amyloidosis. However, with the diagnosis of AL amyloidosis known, we can understand her symptomology better. Her purpuric rashes were due to vascular fragility secondary to amyloid deposits in the endothelium, and it affects up to 15% of patients with AL amyloidosis[8]. Her episode of rectal bleeding was due to amyloid deposition in the gastrointestinal tract (GI), which although common rarely presents as GI bleeding[9]. It can cause chronic obstruction and mucosal ischaemia frequently affecting the descending or sigmoid colon; this would explain the stricture seen in her sigmoid colon and the biopsy results suggesting ischaemic colitis[2]. Her gradually developing symptoms and signs of CCF (including progressive dyspnoea) were due to progressive cardiac amyloid deposition with renal deposition possibly contributing to fluid retention and overload. Indeed, the two most common organ systems affected by AL amyloidosis are the heart and kidneys (40-50% and 30-40% respectively)[2]. Her lytic bone lesions and presence of 21% abnormal plasma cells on bone marrow biopsy would suggest that her AL amyloidosis co-existed with myeloma, which is considered rare compared to co-existence with monoclonal gammopathy of uncertain significance (MGUS)[2,7,8].

Amyloid proteins are basically fragments of normal antibody molecules produced by plasma cells in the bone marrow[1]. Thus, there are screening biochemical tests available to aid diagnosis. These include serum and urine electrophoresis, immuno-electrophoresis and immuno-fixation. Simple electrophoresis is inadequate as many patients (up to 1/3) do not have intact immunoglobulin molecules and only free light chains[5]. Immunofixation can detect monoclonal light chains in 90% of cases[2,5]. Newer techniques include nephelometric assays which are specific for κ and λ immunoglobulin free light chains. The gold standard for diagnosis involves biopsy and staining. Any affected tissue or organ can be biopsied. This can include invasive endomyocardial, renal and liver biopsies (with inherent possible complications) or less invasive subcutaneous (usually abdominal) fat aspiration and bone marrow biopsies[2,5,8]. Because amyloid fragments are carried in the bloodstream, biopsy of any tissue with blood vessels (eg rectum, skin, fat, salivary glands, gingiva) can detect amyloid deposits[2,5,8]. Bone marrow biopsy and fat aspiration can detect amyloid in 50-60% and 70-80% of cases respectively[5]. Of course, all the biopsied specimens need to be stained with Congo Red, which is specific for amyloid[5].

In patients with primary cardiac involvement, cardiac investigations may yield abnormalities, but these are

frequently non-specific. The electrocardiogram may be low voltage with poor R wave progression or depict extreme axis deviations in absence of bundle branch blocks[10]. Echocardiography usually shows ventricular thickening (usually concentric) instead of dilatation[10]. There is also infiltration of the walls and valves which causes increased echogenicity, seen as abnormally 'bright' myocardium described as the classic 'granular sparkling' appearance. Doppler studies usually show a restrictive transmitral flow pattern (short deceleration of E wave and low velocity A wave)[10]. Cardiac catheterisation is usually unhelpful in diagnosing cardiac amyloidosis other than to provide a route to obtain biopsies.

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