Diagnosing light chain (AL) amyloidosis on temporal artery biopsies for suspected giant cell arteritis

Running title: Light chain (AL) amyloid on temporal artery biopsies

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Abstract

Although still rarely diagnosed, light chain (AL) amyloidosis is the most common form of systemic amyloidosis. It is characterized by misfolded monoclonal immunoglobulin light chain fragments that accumulate extracellularly as amyloid fibrils, with consequent organ dysfunction. We report two such cases where initial symptoms and signs were identical to, and mistaken for, those of giant cell arteritis (GCA), associated with polymyalgia rheumatica (PMR). Neither patient responded to high dose corticosteroids; instead, their temporal artery biopsies revealed amyloid deposits and other investigations confirmed a diagnosis of systemic AL amyloidosis. Review of the literature reveals similar cases of diagnostic confusion spanning 75 years. We have summarized the findings and learning points from cases reported in the last 30 years, and highlight the need for increased awareness and investigation of this under-recognized syndrome.

Light chain (AL) amyloidosis typically presents with renal, cardiac, hepatic and peripheral or autonomic nervous system impairment. However, recent guidelines acknowledge marked clinical heterogeneity. AL amyloidosis with symptoms mimicking giant cell arteritis (GCA) or myalgia and fatigue simulating polymyalgia rheumatic (PMR), is not a new phenomenon but it is unusual. We present two cases of AL amyloidosis masquerading as giant cell arteritis, and review the literature since 1986 (1). We draw attention to the similarities and distinguishing features of AL amyloidosis versus GCA.

Case Reports

Patient 1

A 67-year-old man with Waldenstrom macroglobulinaemia experienced myalgia weight loss, fatigue, jaw claudication and sudden visual loss in the left eye. Visual acuity in the left eye was 20/80, with a left relative afferent pupil defect (RAPD) and left optic disc pallor with blurring of the nasal margin. His C-reactive protein (CRP) was 39 mg/L (normal: < 5 mg/L) and platelets were 520,000/ microlitre (normal: 150,000 - 400,000/ microliter). Temporal artery biopsy was not performed but the patient received Prednisolone (1mg/kg) for a presumed diagnosis of arteritic anterior ischemic optic neuropathy. With this treatment, there was minimal improvement in his vision and his other symptoms persisted.

Because of severe myalgia, the patient underwent magnetic resonance imagine (MRI) of the quadriceps muscles. The findings were suggestive of myositis, and a muscle biopsy stained positive with Congo red (Fig 1A) and showed apple green birefringence under polarized light (Fig 1B), diagnostic of the presence of amyloid. The patient was referred to the National

Amyloidosis Center (NAC), where immunostaining of the muscle biopsy was positive for antibodies to kappa light chains (Fig 1C) and negative for antibodies to lambda light chains (Fig 1D). Transthyretin deposition was excluded and kappa light chain type amyloid was confirmed by liquid chromatography mass spectrometry (LC-MS) and proteomic analysis. Further investigations showed: no visceral amyloid deposits by ^{123}I serum amyloid P component (SAP) scintigraphy; no cardiac involvement by echocardiography; and no evidence of amyloid on bone marrow or renal biopsies.

Eight months after left visual loss, the patient experienced sudden loss of vision in his right eye. Visual acuity was 20/200, right eye, and light perception, left eye, with a left RAPD. The right optic disc was pale and swollen and left disc was atrophic. CRP was 93 mg/L and platelet count was 180,000/ microliter. A right temporal artery biopsy was performed, showing eosinophilic infiltrates and focal inflammation within the media (Fig 2A), confirmed as amyloid with Congo red staining (Fig 2B), and no evidence of giant cell arteritis. The patient developed diarrhea, breathlessness, hypotension and edema. He commenced Rituximab, Bortezomib, and Dexamethasone, but died during his first treatment cycle.

Patient 2

A 69-year-old man with a 35 year history of IgD kappa monoclonal gammopathy of undetermined significance (MGUS) with a stable paraprotein of 5g/L and ankylosing spondylitis, was referred to the rheumatology service for symptoms of myalgia, fatigue, global weakness, jaw claudication and scalp tenderness. Recently, he had been investigated for paraesthesias and diagnosed with carpal tunnel syndrome and axonal neuropathy. His CRP was 33 mg/L and platelet count was 486,000/microliter. Duplex ultrasonography of the temporal arteries revealed

arterial wall edema (hyperechoic "halo") consistent with arteritis, normal velocities and no stenosis (2). He was diagnosed with GCA and PMR and treated with high dose steroids without symptomatic relief. Therefore, he underwent temporal artery biopsy which stained positively with Congo red (Fig 3A), showing apple green birefringence in polarized light (Fig 3B) and orange fluorescence under tetramethylrhodamine isothiocyanate (TRITC) filter (Fig 3C). Immunostaining was positive for antibodies to kappa light chains (Fig 3D) and negative for antibodies to lambda light chains (Fig 3E). No transthyretin was detected. Giant cells were present as a foreign body reaction to amyloid deposits, but not centered upon the internal elastic lamina as in giant cell arteritis. Cardiac involvement was detected on MRI. The patient had lytic bone lesions, renal impairment, hypercalcemia and anemia. His bone marrow confirmed myeloma, with up to 90% plasma cells and evidence of amyloid with Congo red staining. At the National Amyloidosis Center, a fat biopsy was positive for amyloid, and ^{123}I serum amyloid P component scintigraphy did not reveal visceral amyloid deposits.

Discussion

Reviewing the literature of AL amyloidosis mimicking GCA yielded 15 reports in the last 30 years (3-16). These are combined with our two patients and summarized in Table 1. These cases illustrate aspects of diagnostic confusion between GCA/ PMR and AL amyloidosis, including clinical findings, investigation results and response to steroid treatment.

A patient with AL amyloidosis involving the temporal artery is likely to fulfill the classification criteria for GCA on a clinical basis in the absence of histology (2). AL amyloidosis may mimic GCA with jaw claudication [(9% of cases (1)] and neuro-ophthalmologic involvement including anterior ischemic optic neuropathy (Table 2). In addition, non-specific

symptoms such as myalgia and fatigue may overlap with those of PMR (17). Patients with a known plasma cell dyscrasia or hematological malignancy and features of 'PMR' should be investigated for AL amyloidosis. This includes histological diagnosis from an affected organ, measurement of serum free light chains, and immunofixation of blood and urine (18).

In AL amyloidosis, amyloid is thought to occlude the arterioles feeding the masseter, causing jaw claudication in a similar manner to lower limb claudication in predominantly vascular amyloidosis (M Gertz, personal communication, April 2016). Estrada et al (9) reported a case of "co-existent GCA and AL amyloidosis"; but giant cells and macrophages were engulfing amyloid depositis. It may be misleading to label this as a case of GCA, preferable instead to refer to it as a secondary arteritis. Because amyloid also may cause arterial narrowing leading to ischemia, Neri et al (14) speculated that ischemic optic neuropathy in AL amyloidosis could be due to reduced adaptability to fluctuations in blood pressure (nocturnal hypotension).

Other areas of diagnostic confusion include laboratory findings, imaging and response to steroids. Raised inflammatory markers (ESR or CRP), thrombocytosis and a normocytic anemia may all be seen in GCA, PMR and AL amyloidosis (12). Dhodapkar and colleagues (19) reported that 60% of their cohort of 93 patients with symptomatic amyloidosis had at least someinitial symptomatic response to high dose steroids. This is another potential factor in delayed diagnosis of AL amyloidosis. Without acknowledging the possibility of an alternative diagnosis, current guidelines for GCA state that patients with negative biopsies should be managed as GCA if there are typical clinical and laboratory features, ultrasound findings and steroid response (20). Several patients in this case series displayed all of these, leading to delayed recognition and treatment of AL amyloidosis. In two cases, amyloid was only identified

on re-staining original temporal artery biopsies with Congo red many months later, showing that deposits are easily missed on H&E staining alone.

It is essential that an experienced pathologist **is** aware of alternate diagnos**e**s when examining temporal artery biopsy specimen**s** as "false negative and false positive diagnoses on the basis of histology are not infrequent" (18). Our paper illustrates the potential perils of overlooking histology, especially in our first patient. Delays in diagnosis and management of AL amyloidosis are a major factor in morbidity and mortality; heightened suspicion of this diagnosis by clinicians is required.

In summary, in suspected GCA (even with neuro-ophthalmic involvement), prompt temporal artery biopsy and Congo red staining is crucial. If GCA is not evident, investigation for an underlying plasma cell dyscrasia must follow; with serum free light chains, immunofixation of blood and urine, and muscle biopsy if features of PMR and known plasma cell dyscrasia. Atypical response to steroids should trigger rapid assessment for AL amyloidosis, with a dose review to avoid unnecessary toxicity.

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Figure Legends

Figure 1. Patient 1. Muscle biopsy stains positively with Congo red (A), and demonstrates apple green birefringence under polarized light (B). There is positive immunostaining for antibodies to kappa light chains (C) but negative for antibodies to lamda light chains (D).

Figure 2. Patient 1. Temporal artery biopsy. A. There are amyloid deposits (dark pink color) in media of vessel walls (hematoxylin & eosin, x 5). B. More extensive deposition of amyloid is seen with Congo red stain (x 5).

Figure 3. Patient 2. Temporal artery biopsy. There are amyloid deposits in the vessel wall detected with Congo red stain. B. This is confirmed as amyloid with appearances of apple green birefringence under polarized light. C. The Congo red stained amyloid fluoresces under tetramethylrhodamine isothiocyanate (TRITC) filter. The biopsy specimen stains positively for antibodies to kappa light chains (D) but not for antibodies to lamda light chains (E).

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