Amyloidosis and Chameleons

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Received: 30 Dec 2021; Accepted: 24 Jan 2022; Published: 28 Jan 2022

ABSTRACT

In this review we presenting two patients who presented with classic manifestations of Amyloidosis. Both were misdiagnosed before amyloidosis progressed and affected other organs causing significant comorbidities.

Keywords
Hypoesthesia, Guillain-Barre syndrome, Neuropathy, Multiple myeloma.

Patient 1

44-year-old male presented with hypoesthesia in both legs, and arms, his medical history included type-II diabetes mellitus on metformin 250 mg BD, his HBA1c was 7.3%, his albumin creatinine ratio A/C was 30mg/mmol in urine (1-3mg/mmol), his fundus examination by ophthalmologist after eye dilation did not show any signs of diabetic retinopathy, patient continued to have pain in his extremities, and was referred to neurologist for leg and arm pain, examination revealed normal strength in both legs and arms, ankle and knee reflexes could be elicited after reinforcement, biceps, triceps and brachioradialis reflex were normal, rest of neurological examination was unremarkable, nerve conduction study was normal, patient was started on venlafaxine.

Two weeks later patient started to develop weakness of legs and arms, which caused him to have a fall. Patient admitted to neurology ward, repeat nerve conduction study showed mixed demyelinating and axonal neuropathy, patient diagnosed as Guillain-Barre syndrome and arranged for skin biopsy proximal to the lateral malleolus for both legs which showed marked decrease in intra-epidermal nerve fiber density and confirmed the diagnosis of small fiber uropathy, patient was started on venlafaxine.

Patient started to develop pain in both hands during night and shortness of breath, examination by general physician showed bilateral carpal tunnel syndrome and signs of heart failure.

Patient was readmitted to the hospital, nerve conduction study diagnosed carpal tunnel syndrome in both hands, echo cardiography showed thickened muscles of both ventricles and atria. Cardiac MRI showed delayed enhancement of the myocardium and diagnosed cardiac amyloidosis. Patient seen by hematologist who arranged for the following investigation, serum and urine immunoelectrophresis, light chain assay, immunophenotyping, abdominal fat biopsy, bone marrow trephine biopsy, SAP Scan, beta 2 macroglobulin, FISH. All after mentioned tests came either negative or normal. Patient did not improve, patient was treated with 40ml/kg.

Plasma exchange for 5 days, with no improvement, repeated nerve conduction study confirmed worsening of Sensomotor length dependent neuropathy; patient was diagnosed with chronic inflammatory demyelinating neuropathy and was started on methyl prednisolone 1 gram IV for 5 days, with no improvement, patient transferred to rehabilitation facility.

More History

Patient gave history that his father and brother died suddenly at the age of 50 due a heart disease. Hematologist arranged a (99mTc DPD scan) which confirmed (transthyretin) ATTR amyloidosis. Rectal Biopsy confirmed ATTR amyloidosis. Biopsy was Congo stain positive, and Congo Biopsy negative.
red positive, biopsy was treated with immunohistochemistry for typing, microdissection and mass spectroscopy confirmed ATTR Amyloid, sequencing for TTR gene ruled out wild type and confirmed ATTR mutant.

Further genetic testing confirmed ATTRV30M. Patient was treated with Tafamidis (new drug to stabilize the TTR tetramer by binding to thyroxine binding sites).

This was followed by liver transplant, patient symptoms improved and he was able to walk and drive his car and live independently.

**Patient 2**

50-year school teacher diagnosed with type 11 DM on diet and metformin, presented to his GP. With symptoms of bilateral carpal tunnel syndrome, for which patient was started on pregabalin with some improvement, patient started to suffer from dizziness and presyncope on standing with a systolic postural drop of 40mmHG, for which GP prescribed fludrocortisone, routine urine testing showed proteinuria with albumin creatinine ratio of 40mg/mmol.

Patient started to experience pain in his legs, neurological examination of the legs by GP was normal. GP prescribed amitriptyline for leg pain and increased the dose of pregabalin to 75 mg BD. With no improvement, patient developed shortness of breath on walking uphill’s, seen by a cardiologist and arranged for coronary angiogram, which did not show any significant stenosis.

Echocardiogram showed marked thickening of the left and ventricle, marked thickening of the interventricular septum, thickening of left and right atrium, normal left ventricular cavity, left ventricular ejection fraction 70%, tissue and color doppler showed impaired longitudinal function, cardiac MRI with gadolinium showed diffuse and irregular delayed enhancement of the myocardium. Patient referred to hematologist for investigation for Amyloidosis.

The following investigation was performed, serum and urine protein electrophoresis, light chain sassy. Immunophenotyping, FISH, rectal biopsy, immunohistochemistry, bone marrow trephine biopsy, SAP Scan, DNA study. Congo red staining for biopsy under polarized light. AL Amyloidosis was confirmed.

Patient was counselled for treatment and treated with high dose of Melphalan and Autologous peripheral blood stem transplantation with complete recovery.

**Discussion**

Amyloidosis is uncommon disease characterized by deposition of abnormal folded protein extracellularly in most tissue of the body causing multi-organ damage. This abnormal misfolded protein is characterized by its affinity for Congo red light and yellow-green birefringence under polarized microscopy [1].

Amyloidosis could be either hereditary or acquired, it is of paramount importance to diagnose and treat amyloidosis early enough before it progressed and became non-treatable [2].

**AL Amyloidosis**

AL Amyloidosis is the most common acquired amyloidosis in developed countries [3]. AL amyloid fibril is derived from immunoglobulin light chain due to plasma cell dyscrasia [4]. AA amyloidosis is the second less common acquired amyloidosis, which is characterized by extracellular deposition of intact serum amyloid A (SAA) (protein that is acute phase reactant complicating chronic inflammatory diseases like Ankylosing Spondylitis, inflammatory bowel disease, bronchiectasis, chronic osteomyelitis, Juvenile rheumatoid Arthritis, familial periodic fever syndrome) [4]. Hereditary amyloidosis could be due to mutated transthyretin, plasma transport protein for thyroxine and vitamin A which are produced by the liver, the other type of hereditary amyloidosis is non mutated wild type transthyretin which used to be called senile amyloidosis because it is commonly affected patients aged 70 or above [5].

**Hereditary Amyloidosis**

Formally called familial amyloidosis encompass transthyretin mutated hereditary amyloidosis and non-mutated wild type hereditary amyloidosis [9], it is characterized by being severe heterogeneous. Disease commonly manifested by autonomic and peripheral neuropathy, infiltrative restrictive cardiomyopathy which commonly misdiagnosed as hypertrophic cardiomyopathy [10]. Autonomic neuropathy commonly cause postural hypotension, gastropathy, bladder and erectile dysfunction. Kidney involvement causing nephrotic proteinuria and kidney failure [11]. Ocular involvement in the form of amyloid retinal angiopathy, vitreous opacification, amyloid deposition in the lens and iris [12].

Hereditary transthyretin amyloidosis can affect the brain causing stroke, subarachnoid hemorrhage, cerebellar ataxia, seizure, deafness, dementia, leptomeningeal amyloid angiopathy, hydrocephalus, spastic paresis, oculoareptomeningeal amyloidosis,
Diflunisal is a nonsteroid anti-inflammatory agent that stabilizes TTR protein and prevent dissociation, of the tetramer [18]. Liver transplant can cure the disease if diagnosis had been made very early before involvement of the heart and nerves, 5-year survival rate is 100% for V30M and 59% for non-ATTRV30M. Successful liver transplant will not reverse neuropathy or cardiomyopathy. Liver transplant is considered as a disease modifying agent and not curative when other organs were affected [19].

**Conclusion**

Systemic amyloidosis is not one disease and can affect most organs in the body, early diagnosis is crucial for optimal treatment, physicians should develop awareness of the spectrum of the disease, which can affect most organs in the body, identifying the fibril type, and provide early treatment can eliminate and reduce the burden of the disease [20].

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