Review Article

Insights in Blood Disorders

Amyloidosis and Chameleons

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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, neve conduction study was normal, neurologist diagnosed small fiber neuropathy 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.

Two weeks later patient started to develop weakness of legs and arms, which caused him to have a fall. Patient admitted in neurology ward, repeat nerve conduction study showed mixed demyelinating and axonal neuropathy, patient diagnosed as Guillain-Barre syndrome and started on IV immunoglobulin 0.4gram/kg for 5 days, with close observation of his forced vital capacity, Lumbar puncture study showed Acellular CSF with elevated protein, 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.

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, Florescence in situ hybridization (FISH). All after mentioned tests came either negative or normal.

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

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 (1 mg/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 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].

AL Amyloidosis

AL Amyloidosis is a serious systemic acquired disease caused by extracellular deposition of misfolded protein in most organs of the body [6]. Due to plasma cell monoclonality which encompass Multiple Myeloma, Monoclonal gammopathy of undifferentiated significance smoldering Myeloma, Waldenstrom Macroglobulinemia. Common organs affected by AL Amyloidosis are heart, kidney, gastrointestinal, liver, central and peripheral nervous system [7], organomegaly, macroglossia. Because of the non specific symptoms that could be easily misinterpreted, diagnosis usually delayed and this causing delay of treatment. Important investigations to be done are tissue biopsy (fat pad, any affected organ, bone morrow) and tissue typing (mass spectrometry, immunofluorescence, immunohistochemistry, immunogold electron microscopy). Cytogenic profile became a standard risk assessment marker of severity and response to treatment [8]. High dose melphalan followed by autologous stem cell transplant is the standard of care for low-risk patients [9]. Patients who are ineligible to autologous stem cell transplant can be treated with Daratumumab-based regimen, Bortezomib based regimen.

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, oculoleptomeningeal amyloidosis,

renovascular amyloidosis [12].

Genetics

120 mutations had been identified; the most common mutation is Val30Met which caused a point mutation leading to replacement of valine by Methionine at position 30 of the mature protein which constitute more than 50% of Transthyretin mutations [13].

The mode of inheritance is autosomal dominant, the penetrance of the disease is variable, and patients can carry homozygous or compound heterozygous mutation. Anticipation is more common in male offspring.

Inheriting the mutation from the mother, father to daughter inheritance had been shown to be protective. Transthyretin protein in mainly formed in the liver, it transports protein to thyroxine and the choroid plexus produce retinal binding protein to retina and ciliary pigment. Genetic counselling for asymptomatic family is essential once mutation had been detected.

Diagnosis usually missed in negative family history, patient commonly misdiagnosed as chronic inflammatory demyelinating neuropathy, diabetic axonal neuropathy, Charcot -Marie tooth disease, motor neuron disease, progressive muscular atrophy, spinal canal stenosis [14].

Early diagnosis of TTR Amyloidosis and treatment with orthotropic liver transplant can lead to permanent cure, as liver is the main source of the mutated misfolded protein [15].

99 Tc-DPD proved to have high sensitivity and specificity for establishing the diagnosis of ATTR Amyloidosis and can show cardiac involvement even with normal ECG, echo and cardiac MRI, [16].

Confirmation of the diagnosis is only made by histological examination, endomyocardial biopsy is indicated if there is no extracardiac involvement, correct diagnosis of the subtype is essential, confirmation of the subtype depends on immunohistochemistry, mass spectrometry, DNA analysis and genetic study. Presence of monoclonal protein should not stop clinician to investigate for ATTR amyloidosis as 5% of population above 65 has monoclonal gammopathy of undetermined significance.

Medical treatment of cardiac amyloidosis is quite challenging, as they are sensitive to diuretics because of decreased preload and autonomic neuropathy. Patients usually could not tolerate beta-blocker, calcium channel blockers or digoxin as they bind to amyloid fibrils and cause toxicity. Cardiac transplant alone does not cause cure in the presence of extra cardiac amyloidosis. Tafamidis approved in Europe for treatment of ATTR mutant amyloidosis. It is a small molecule that binds to TTR at T4 binding sites causing stabilization of the protein and preventing its dissociation and precipitation in body organs [17].

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 V3oM and 59% for non-ATTRV3oM. 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, phycisions 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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