Large Pericardial Effusion : A Clinical Dilemma!

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Abstract

A 55yr old gentleman known diabetic and hypertensive presented with breathlessness and tingling sensation of both upper and lower limbs with strong family history of similar neurological problems. On extensive evaluation he was found to have amyloidic peripheral neuropathy with large pericardial effusion. Tubercular etiology was confirmed by pericardial fluid PCR and culture. Here the diagnostic dilemma was whether Amloidosis is primary, secondary to Tubercular pericardial effusion or Hereditary Amyloidosis. In the end, how we have arrived at the diagnosis of Hereditary Amyloidosis based upon the strong family history and nerve biopsy is interestingly presented in the following case report.

A 55yr old man, known case of hypertension and Type2 DM presented with breathlessness on exertion for the past 2yrs associated with PND. He also had difficulty in climbing upstairs with weakness of both lower limbs since 2yrs. He had difficulty in getting up from squatting position and for the past 6months he noticed that there is slipping of foot wear of which he is not aware. There is tingling sensation of both feet up to mid thighs and forearms up to elbows. He also had numbness of both hands and feet with sensation of cottonwool while walking. History of erectile dysfunction with occasional fecal incontinence was present.

Family history was very much significant with similar neurological problems noticed in his maternal grandfather, mother, brother and his brother’s son. No clinical documents were maintained.

On examination he had postural hypotension with supine BP of 160/100 and standing BP of 110/80, bipedal pitting edema, healed ulcers over both shins with no thickened nerves. His cardiovascular system examination showed raised JVP and normal heart sounds. On CNS examination he had wasting of interosseus and hypothenar muscles on both sides, weakness of finger abduction of both hands, feet dorsiflexion, toe dorsiflexion, plantar flexion and toe grip. Sensory examination showed graded sensory loss to touch and pain up to mid thigh and forearms up to elbows. All deep tendon reflexes were absent with plantars normal. Coordination and gait were normal. His abdomen showed moderate to severe ascites with no visible veins over abdomen. Hepatomegaly was present 5cms palpable below midcostal line. He has undergone suprapubic cystostomy with silicon bladder catheter because of atomic bladder. His lung fields were clear on auscultation with no added sounds.

His basic investigations showed decreased hemoglobin (12 gm%), PCV (35.87%), MCV (77.3 fl) suggestive of dimorphic blood picture with total count on lower side of normal (5100 cells/cm³). Blood urea (19 mg%), serum creatine (0.7 mg%), sodium (140 mEq/L), potassium (3.8 mEq/L) were normal. Serum protein (5.7 gm%) and albumin (2.9 gm%) were lower with normal liver enzymes and bilirubin. Serum protein electrophoresis was normal except for decreased albumin (0.9 gm%). His thyroid function tests were normal (TSH-2.03 IU/l, T3-1.03 ng/ml, T4-8.62 mcgm/dl). Serum B₁₂ level was normal (1694 pg/ml). Abdominal ultrasound showed hepatosplenomegaly with diluted IVC and hepatic veins and moderate to severe ascites with mild left pleural effusion Urinary Bence Jones protein was not detected. ECG showed normal sinus rhythm with low voltage complexes. On echocardiography there was large diffuse pericardial effusion, concentric left ventricular hypertrophy and normal biventricular function (Figure 1). Doppler echo showed no restrictive filling pattern. Cardiac MRI showed concentric hypertrophy of left ventricle with pericardial effusion and no mass lesion. There was no late contrast enhancement of myocardium (Figure 2). On coronary angiography there was insignificant coronary artery disease with stenosis of RCA of 30%. CT scan of the chest showed pericardial effusion. Abdominal and pelvic CT showed moderate ascites with no focal enhancing lesion in liver. CSF analysis showed mildly increased glucose and protein (glucose-70 mg%, protein-103 mg%) with normal counts. MRI brain study was normal. There was mild parasympathetic, moderate sympathetic and moderate autonomic nervous system dysfunction on autonomic function studies. Nerve conduction studies showed peripheral nerve involvement with mixed demyelination and axonal degeneration. On nerve biopsy there was asymmetric small fibre loss with fluffy perivascular eosinophilic material deposited which is congophilic and birefringent. Serum was negative for HIV, HBsAg, HCV and VDRL. Genetic test for Transthyretin was negative. Rectal biopsy from eight multiple sites showed mild nonspecific inflammation with no evidence of amyloid deposition.

Under fluoroscopic guidance, pigtail catheter was introduced into the pericardial space and around 800 ml of straw colored fluid was drained. Pericardial fluid analysis showed a cell count of 100 cells/cms³ with predominant lymphocytes. Cell block study showed absent malignant cells. Fluid was exudative with increased LDH and albumin compared with serum. Culture was negative for bacterial growth. PCR test of pericardial fluid for Mycobacterium Tuberculosis Complex (M. tuberculosis and M. bovis) was detected. Subsequently pericardial fluid on culture showed growth for Mycobacterium tuberculosis. RA factor and ANA were negative.

He was started on ATT, steroids, sugar control with insulin and ACE inhibitors for hypertension.

Discussion

On analysis of clinical features and laboratory tests it is clear...
that this patient is suffering from chronic symmetric small fibre peripheral neuropathy, large tubercular pericardial effusion associated with strong family history of peripheral neuropathy on background of long standing hypertension and Type2 diabetes mellitus. Nerve biopsy confirmed it to be Amyloidosis. Here the diagnostic dilemma is whether Amyloidosis is primary, secondary to Tubercular pericardial effusion or is Hereditary Amyloidosis.

There are two major forms of acquired systemic amyloidosis. The first, systemic amyloid A (AA) amyloidosis, is associated with chronic inflammatory diseases (eg. rheumatoid arthritis, tuberculosis) and amyloid deposits in the kidneys, liver, and spleen. The fibrils are derived from circulating, acute-phase reactant serum amyloid A protein. The second, formerly known as primary amyloidosis, is caused by the accumulation of monoclonal immunoglobulin light chains as amyloid fibrils and is now referred to as AL amyloidosis. In this disease, clonal plasma cells produce the light chains, which polymerize as amyloid fibrils in the kidneys, heart, liver, intestines, skin, autonomic and peripheral sensory nervous system, spleen, and lungs. The possibility of AL amyloidosis must be considered in any patient with unexplained nephrotic syndrome, renal insufficiency, congestive heart failure, sensorimotor peripheral neuropathy, and monoclonal immunoglobulins or light chains in the serum or urine.1 The kidney is the most frequent site of amyloid fibril deposition in both immunoglobulin light chain (AL) amyloidosis and serum amyloid A (AA) amyloidosis, and this condition is typically manifested as the nephrotic syndrome.3,6 So in both AL and AA amyloid multiple organs are involved and kidney is most frequently involved with nephrotic syndrome.1,6 In our case kidney function is normal with normal 24hr urinary protein. Serum electrophoresis did not show monoclonal immunoglobulins or light chains. The salient cardiovascular feature in this case was thickening of the myocardium. When an echocardiogram shows thickening of the ventricular myocardium in a patient without hypertension, an infiltrative process, such as amyloidosis, should be considered.4 But here the patient has hypertension and doppler echo does not show restrictive filling pattern. Further cardiac MRI did not show late contrast enhancement which is very specific for amyloidosis. So isolated peripheral nerve involvement as in our case is very rare in AL and AA amyloidosis and it is very unusual for the kidney and other systems not to be involved during the course of two years.3,6 Considering these things the possibility of AL and AA amyloidosis were ruled out. Because of slow progression of the disease with isolated peripheral nerve involvement and strong family history, we strongly considered the possibility of Hereditary neuropathic amyloidosis. In our case transthyretin which is most commonly involved with Hereditary neuropathic amyloidosis is negative, probably because transthyretin variant might be involved here.1,2

So the final diagnosis is hereditary neuropathic amyloidosis with large tubercular pericardial effusion

Seven proteins have been associated with hereditary systemic amyloidosis: transthyretin, apolipoproteins A-I and A-II, gelsolin, cystatin C, the a-chain of fibrinogen A, and lysozyme.2,7 Some of these hereditary forms of amyloidosis are neuropathic, whereas others are cardiomyopathic, and still others are associated with nephropathy. The autonomic and peripheral nervous system, the heart, or the kidneys may be the sole or the principally affected site. Transthyretin is the most common amyloidogenic protein in familial disease. In senile systemic amyloidosis, wild-type transthyretin forms amyloid deposits predominantly in the heart. Here senile amyloidosis is ruled out because of the younger age of the patient. Genetic analysis can be used to assess the hereditary amyloidoses. However, there are more than 20 proteins that can form amyloid, and for many of them, multiple amyloid-inducing mutations have been discovered. Biochemical techniques primarily liquid chromatography and mass spectrometry have been applied to identify amyloidogenic proteins. Although still experimental, these new techniques may become the gold standard for the sub classification of amyloid deposits. The presence of amyloid in tissue is not always readily apparent, and pathologists frequently do not recognize it on examination of sections routinely stained with hematoxylin and eosin.4,5 The results of the rectal-pad biopsy here in this case were negative, could be because of the process has involved just the nervous system and in due course of time may involve other system also and also involvement of intestine is very rare in Hereditary neuropathic amyloidosis. The patient was reluctant to undergo a more invasive diagnostic procedure like cardiac and renal biopsy. The diagnosis of type of amyloidosis is very important because the treatment differs. AL amyloidosis often responds to chemotherapy that suppresses the underlying clonal plasma-cell disorder, but chemotherapy has no role in the treatment of hereditary amyloidosis and is dangerous. The types of hereditary amyloidosis in which the amyloidogenic protein is synthesized solely by the liver can be effectively treated by liver transplantation. This form of “surgical gene therapy” has been successful in familial amyloid polyneuropathy associated with variant forms of transthyretin and in amyloidosis due to the Glu526Val variant of fibrinogen A a-chain.

Here the patient was explained about the need for...
genetic testing of his children. He is not affordable for liver transplantation, and was sent home with conservative management.

References