ORIGINAL RESEARCH PAPER

Haematology

A CASE SERIES ON AMYLOIDOSIS IN A TERTIARY CARE CENTRE

KEY WORDS:

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ABSTRACT

Amyloidosis is a systemic disorder with varied presentation involving multiple organs. AL amyloidosis is a clonal plasma cell disorder. Here we discuss three cases of amyloidosis, diagnosed and treated in tertiary care centre highlighting the wide spectrum of presentation and diagnostic challenges. First case, 70 year old female presented with volume overload status with nephrotic range proteinuria diagnosed as primary AL amyloidosis. Second case presented with restrictive cardiomyopathy and renal involvement and Third case presented as a peripheral neuropathy.

2. INTRODUCTION

The precise incidence of AL amyloidosis is unknown. Older persons are more susceptible to AL amyloidosis. Patients with MM and WM, which are malignant disorders of plasma cells can develop AL amyloidosis. Less commonly, marginal zone lymphoma or another non-Hodgkin lymphoma subtype may be linked to AL amyloidosis. Chemotherapy is used to treat AL amyloidosis since it is a clonal plasma cell condition. Since other kinds of amyloidosis, such as AA amyloidosis, ATTRmt amyloidosis, and ATTRwt amyloidosis, are non-neoplastic and will not respond to chemotherapy, AL amyloidosis must be distinguished from these other forms

3. AIM AND OBJECTIVES

Amyloidosis is a rare condition and high degree of suspicion in patients with in non diabetic nephrotic syndrome, non ischemic cardiomyopathy and hypertrophy and hepatomegaly or increased alkaline phosphatase in myeloma patient, increased NT Pro BNP in the absence of known primary heart disease and unexplained carpal tunnel syndrome. Chemotherapy is available as treatment. Here we discuss three cases of amyloidosis with detailed clinical history, evaluation and management.

4. Review of Literature

The term amyloid means "starch like". Amyloidosis is a protein misfolding or conformational disorder which deposits extracellularly in organs. misfolded proteins assume antiparallel, beta pleated sheet rich conformation that leads to the formation of higher order oligomers. There are atleast 38 different human proteins that can develop into amyloid fibrils. Localized amyloid is created at the site of amyloid formation, and blood-borne amyloid circulates to deposit in a range of tissues and organs (systemic amyloidosis). Using polarized light microscopy on Congo red-stained tissue, amyloid exhibits birefringence. Amyloid tissue may appear "apple-green" dichroic. Point mutations, deletions, and premature stop codons may cause structural alterations that make these proteins more likely to form fibrils (fibrillogenesis) and generate amyloid.

AL amyloid - Protein produced from immunoglobulin light chain fragments is deposited. Associated with plasma cell dyscrasia. ATTR amyloid - ATTR amyloid can be "wild-type" (ATTRwt), which is linked to ageing, or it can be a mutant protein (ATTRv or hATTR, where v stands for a variant and h for hereditary; these were formerly referred to as ATTRm, to denote a mutant protein), which is linked to familial neuropathy and/or cardiomyopathy.

Acute phase reactant serum amyloid A protein, which can form amyloid deposits, is produced in high level in chronic inflammatory. This condition is known as AA amyloidosis. Clinical presentation: Renal: nephrotic range proteinuria; Cardiac: restrictive cardiomyopathy. Low voltage QRS complexes with pseudoinfarct pattern; Nervous system: autonomic dysfunction, carpal tunnel syndrome, cerebral amyloid angiopathy; Gastrointestinal: macroglossia-pathognomic clinical sign Hematological: raccoon eyes due to abnormal clotting and coagulation abnormality. Diagnosis: The presence of amyloid fibrils during histologic examination of an affected organ (such as the kidney or liver) or a substitute site is necessary for the diagnosis of AL amyloidosis (eg, abdominal fat pad, bone marrow). The presence of amyloid fibrils can be confirmed by their characteristic appearance on electron microscopy. The type of amyloidosis can be identified by immunohistochemical staining of the amyloid (for example, for kappa and lambda light chains, transthyretin, and serum amyloid A component). Less than 50% of patients with AL amyloidosis will have a localised band or peak on serum protein electrophoresis (SPEP), which detects intact monoclonal immunoglobulin. In approximately 90% of instances of AL amyloidosis, M proteins can be found in the serum or urine using immunofixation procedures meant to identify light chains. An M protein can almost always be found when serum and urine immunofixation is coupled with serum free light chain ratio analysis.

A technique called serum amyloid P component (SAP) scintigraphy uses a radiolabeled form of the SAP present in all amyloid deposits to assess the degree of amyloid involvement. Treatment: Use of induction therapy followed by high dose melphalan and autologous HCT for patients who are fit enough, rather than HCT or chemotherapy alone. Preferred induction therapy is daratumumab plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD). For AL amyloidosis, CyBorD is usually administered on a 28-day cycle as follows: Bortezomib 1.3 to 1.5 mg/m2 subcutaneous administration once a week, Cyclophosphamide 500 mg (total dose) orally once a week, Dexamethasone 20 to 40 mg orally once a week

5. MATERIAL AND METHODS

CASE 1

A 70-year-old female known case of hypertension presented with complaints of bilateral leg swelling and difficulty in breathing. On examination, bilateral pitting pedal oedema was present. Systemic examination was normal. Routine investigations: CBC- normal. Urea-44.5 creatinine 0.96: Urine

albumin 4+(dipstick). Urine PCR-6.94. 24 hours urinary protein-3850mg/dl. ECHO- normal study. In view of nephrotic range proteinuria renal biopsy was planned Patient USG revealed grade 1 medical renal disease. ANA- negative. C3 C4 normal. Albumin was 1.5; total protein 4.6; Triglyceride:196 mg/dl; Total cholesterol: 362mg/dl. Renal biopsy showed diffuse and global positivity for lambda 3+ and negative for c3 c1q, kappa, IgG, IgA, IgM- IMPRESSION: amyloidosis AL type Urine Bence jones protein negative. SPEP: hypogamma globulinemia with increase in beta 1 globulins and M band in beta 1 globulin. Bone marrow showed cellular marrow with 6% plasma cell with lambda restriction Serum free light chain lambda-155(increased). Normal serum free kappa and normal kappa/lambda ratio. Case was diagnosed as Primary AL Amyloidosis and started on chemotheraphy.

Case 2:

A 55 year old female, a known case of hypothyroidism presented with c/o bilateral leg swelling for 6 months and breathlessness on exertion for 5 months. she was apparently asymptomatic one year ago after which she developed significant loss of weight for one year, loss of appetite and loss of hair for one year then she developed bilateral leg swelling - past 6 months which was insidious in onset and progressive, extending till knee. History of abdominal distension for the past 5 months – diffuse, insidious onset, gradually progressive, not associated with pain. c/o breathlessness on exertion for 5 months – insidious onset, gradually progressive, NYHA grade 2 at present. h/o orthopnea present c/o palpitations on exertion – 5 months. On examination, patient was conscious, oriented, afebrile , thin built, poorly nourished ,alopecia present , pallor present, bilateral - grade 2 pandigital clubbing present, bilateral pitting pedal edema present till knee. Vitals: BP: 110/70 mmhg in right upper limb in sitting position, pulserate – 92 /min, respiration- 16/min, CBG- 112 mg/dl, JVP –10 cm. CVS – s1, s2 present, no murmur.RS- B/L AE +, decreased air entry in left intrascapular and intraaxillary areas , vocal fremitus and vocal resonance decreased in left intrascapular region and left infraxillary region, dull note on percussion in left infrascapular and infraxillary areas, normal vesicular breath sounds in all other areas. P/A–uniformly distended. liver was palpable 5 cm below right costal margin, tender, surface – smooth. liver span – 14 cm. Investigation: HIV – negative, HbsAg – negative, HCV antibody – negative Lipid profile: Total cholesterol – 305mg/dl; Triglyceride- 150mg/dl; LDL – 199mg/dl TSH: 8.24: Free t3: 2.35, free t4: 1.02 Urine analysis: albumin: 4+ pus cells – less than 5 urine PCR: 3.12: 24 hours urine protein: 3.2g chest Xray-left pleural effusion, Ultrasound abdomen: liver: mild hepatomegaly (14cm), left sided pleural effusion, right renal cortical cyst, ascites. ECHO: concentric LVH, normal LV systolic function, mild pericardial effusion, mild mr, mild TR, tricuspid and mitral valve movements restricted, LA and RA dilated, restrictive cardiomyopathy. ANA – negative. Renal biopsy light microscopy: Glomeruli observed, none are sclerotic with acellular, amorphous, eosinophilic pas and silver negative material is observed in the mesangial, glomerular capillary loops and blood vessel. Special staining and immunofluorescence: the material is Congo red positive and gives apple green birefringence, lambda light chain restriction is seen in glomerular mesangium and blood vessels. Features suggestive of AL amyloidosis. Urine Bence jones protein – negative. Serum protein electrophoresis: normal Bone marrow biopsy section shows linear coarse of bony trabeculae showing moderately cellular marrow composed of scattered megakaryocytes of normal maturation and morphology. Cellularity normal; normoblastic maturation; plasma cells < 1%

Case 3

70 years female came with complaints of blackish discoloration of periorbital region for past 1 week, easy fatiguability and loss of weight and apetite for past 2 months, bilateral lower limb paresthesias past 3 months. Systemic examination was normal. Routine investigation: CBC showed normocytic normochromic anemia Urea 60 mg/dl serum creatinine – 1 mg/dl urine albumin – nil Usg abdomen- mild hepatomegaly. ECHO-normal. ANA – negative NCS showed bilateral sensory and motor axonal neuropathy. Abdominal fat biopsy : section showed fibrofatty and fibrocollagenous stroma exhibiting strands of amorphous, acellular, eosinophilic material. Some of them are seen around blood vessels. Stroma shows thin walled congested blood vessels and hemorrhage. Special staining: congo red – positive in eosinophilic amorphous material. Impression : Amyloid deposition in abdominal fat. PET CT whole body scan : bilateral minimal pleural effusion. No evidence of metabolically active lytic/ sclerotic lesion in axial/ appendicular skeletal system. No evidence of metabolically active disease elsewhere in the body.

6. RESULTS (Including Observations)

The diagnosis of first two cases were made since the presentation was common. Even though there were evidence of light chain deposition in renal biopsy, serum and urine electrophoresis could not establish M protein. Hence a follow up investigation is important in such cases. The third case with an index of suspicion we took an abdominal fat biopsy and turned to be positive for Congo staining.

7. DISCUSSION

Amyloidosis is a systemic disorder characterized pathologically by the extracellular deposition of insoluble fibrils composed of misfolded proteins in various organs including the heart with resulting alteration in structure and function. The amyloid fibrils are rigid, proteolytic resistant structures, typically less than 10 nanometers in diameter with a characteristic apple-green birefringence with Congo-red staining under polarized light microscopy. Amyloidosis may be hereditary or acquired and the nature of the precursor protein of the fibrils forms the basis of classification. More than 30 such precursor proteins have been identified and of these, 2 types are responsible for about 95% of cases of cardiac amyloidosis: Immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). AL, although overall a rare condition, is the most frequently diagnosed. AL occurs secondary to a plasma cell dyscrasia resulting in excessive production of immunoglobulin light chain units, with associated misfolding and deposition in extracellular tissue. In addition to cardiac manifestations, hepatic, renal and neurologic complications may be seen in AL. Early diagnosis and initiation of treatment in AL may alter disease outcome although mortality remains high. ATTR occurs due to the misfolding of the liver derived precursor protein transthyretin (TTR, previously called prealbumin).

TTR has a tendency to dissociate into dimers and monomers and subsequently aggregate into insoluble fibrils. Two variants of this form of amyloidosis have been described – the hereditary/mutant form caused by mutations in the TTR gene and the sporadic/wild type (systemic senile amyloidosis). Atleast 38 different human protein precursors of amyloid fibrils are known.

Some are produced at the site of amyloid formation (localized amyloid) and some circulate in the body to deposit in a variety of tissues and organs. Amyloid has a characteristic gross pathologic and microscopic appearance, demonstrating birefringence with polarized light microscopy of Congo red stained tissue which may have a typical apple green dichroic appearance

8. SUMMARY AND CONCLUSION

There are 2 main approaches to treating the underlying amyloidosis – stopping further production of the precursor protein and reducing the burden of already deposited amyloid. With an increasingly ageing population and

advances in cardiovascular imaging techniques, conditions that previously went undiagnosed and thought to be uncommon are being increasingly identified. Cardiac amyloidosis is one of such conditions. In addition, with broad research ongoing on various modalities of treatment, early diagnosis may be crucial to limiting further amyloid deposition and thus, alter the disease course. Amyloidosis remains a rare disease despite a recent uptick in diagnoses owing to increased physician suspicion. With emerging therapies that have the potential to improve patient outcomes, early diagnosis has taken on an increasingly important role.

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