Section: Clinical Haematolgy

Original Research Article

STUDY OF CLINICO-DEMOGRAPHIC PROFILE AND DIAGNOSTIC PARAMETERS IN PRIMARY AMYLOIDOSIS

Vikram Yelugoti[1], A Karthikeyan[2], Vandana G Hari[3], Aruna R[4], Divya M[5]

[1] Senior Resident, Department of Clinical Haematolgy, Madras Medical College, Chennai, Tamil Nadu, India.
[2] Associate Professor, Department of Clinical Haematolgy, Madras Medical College, Chennai, Tamil Nadu, India.
[3] Senior Resident, Department of Clinical Haematolgy, Madras Medical College, Chennai, Tamil Nadu, India.
[4] Assistant Professor, Department of Clinical Haematolgy, Madras Medical College, Chennai, Tamil Nadu, India.
[5] Senior Resident, Department of Clinical Haematolgy, Madras Medical College, Chennai, Tamil Nadu, India.

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Corresponding Author:
Dr. Vikram Yelugoti
Email: vikramyelugoti@gmail.com

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Abstract

Background: Primary Amyloidosis is a systemic, rare plasma cell dyscrasia in which insoluble amyloid proteins are deposited in the body organs, eventually leading to organ dysfunction and death. The heart, kidneys, nerves and gastrointestinal system are the most common organs affected. Our study aims to shed light on the clinicodemographic profile and diagnostic parameters of primary amyloidosis in a tertiary care hospital. **Materials and Methods:** A retrospective study was conducted at Rajiv Gandhi Government General Hospital, Chennai, Tamil Nadu, from December 2020 to November 2022 on 18 biopsy-proven cases of primary amyloidosis. The objectives were to identify and categorise the presenting symptoms and elucidate the demographic profile. **Result:** In total, 18 cases were identified for two years. Males were the gender most commonly affected by the condition (11 cases). Most instances were between the ages of 51 and 60; the youngest was 38 years old, and the oldest was 71 years old. Fatigue (77%), edema (72%), weight loss (27.7%), diarrhoea (11.11%), and shortness of breath (16.6%) were the symptoms that were present. Renal involvement was most frequently prevalent in 10 cases (55.5%). **Conclusion:** Primary Amyloidosis is a rare disorder of plasma cells with varied presentations leading to organ dysfunction. A thorough understanding of the clinical course of the disease and a high degree of clinical suspicion is required for early diagnosis and treatment.

INTRODUCTION

Primary amyloidosis is a systemic, rare plasma cell dyscrasia characterised by accumulated insoluble amyloid proteins in human organs, eventually leading to organ malfunction and death. The term "amyloid", coined by Rudolph Virchow, refers mostly to extracellular deposits of a fibrillary protein that are distinguishable by their affinities for Congo red and their apple-green birefringence under polarised light, according to the International Society of Amyloidosis (ISA) criteria.[1,2] Approximately 60 different amyloidogenic proteins have been found, with more than 32 of them being linked to known human diseases. The ability of these proteins to produce beta-pleated sheets aligned in an antiparallel pattern is what connects them. These sheets subsequently form inflexible, nonbranching fibrils that are resistant to proteolysis and induce mechanical disruption and local oxidative stress in organs such as the heart, liver, kidneys, and gastrointestinal system.[3]

Amyloid deposits can be localised or systemic, with the former affecting a single organ and the latter affecting multiple organs and tissues across the body. AL amyloidosis (light chain; previously also called primary amyloidosis) is caused by clonal plasma cell disease, with an annual incidence of 10 per million. The condition is caused by a bone marrow plasma cell clone (rarely a B-cell clone) that secretes an unstable, amyloidogenic immunoglobulin light chain (LC). The kidneys (74%), heart (60%), gastrointestinal tract (10-20%), liver (27%), and autonomous nervous system (18%) are the most commonly affected organs. 69% of

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patients have more than one involved organ at the time of diagnosis.[4]

Biopsy of a clinically afflicted organ is the most sensitive approach for detecting amyloidosis and may uncover concurrent diseases. However, a kidney or heart biopsy is an intrusive procedure that might result in bleeding. If amyloidosis is clinically suspected, a less invasive method, such as subcutaneous fat aspiration biopsy, rectal or stomach mucosa biopsy, or salivary gland biopsy, is preferable. Combining subcutaneous fat pad aspirate and bone marrow biopsy, approximately 85% of light chain amyloidosis will be identified. Amyloidosis staging entails distinguishing between systemic and localised amyloidoses and determining which organs are involved. Survival is mostly determined by cardiac involvement. Organ dysfunction advances and ultimately results in mortality if the disease is not promptly and adequately treated. The best care for individuals with AL amyloidosis requires an early diagnosis, accurate classification of the type of amyloid, successful treatment with supportive medication, and meticulous follow-up.[2,3,4,5,6]

MATERIALS AND METHODS

A retrospective descriptive analysis of 18 individuals diagnosed with primary amyloidosis was conducted at Rajiv Gandhi Government General Hospital in Chennai, Tamil Nadu, spanning two years from December 2020 to November 2022. The information came from the patient's medical records. There were no extra tests or interventions performed for the study. Only cases of amyloidosis proven by tissue biopsy were considered for the study. Multiple myeloma with secondary amyloidosis was excluded from the study. A structured proforma was prepared, and data was recorded. Age and gender statistics for patients were noted. The various presenting complaints were recorded and tabulated. Organ involvement was also noted. Serum protein electrophoresis (SPEP) test analysis was noted. Serum-free light chain (SFLC) testing results was also recorded. (Echocardiography) ECHO findings were also noted. SPSS (Statistical Package for the Social Sciences) 20 for Windows was used to analyse the results, and descriptive analyses were performed.

RESULTS

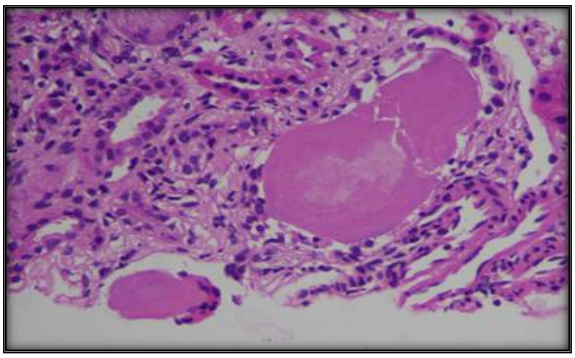

Figure 1: 40x photomicrograph of renal biopsy showing homogenous eosinophilic deposits suggestive of amyloid

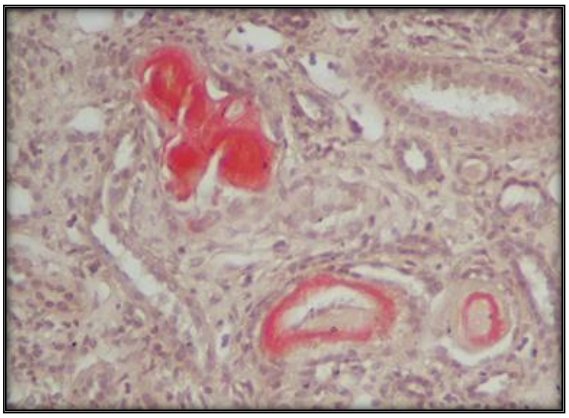

Figure 2: Photomicrograph of renal biopsy showing amyloid deposits positive for congo red stain

During the study period, 18 cases of primary amyloidosis were diagnosed. There were 11 males and seven females among the 18 cases, for a male-to-female ratio of 1.5:1. The ages of study participants varied from 38 to 71 years, with a mean of 51.2 years. Fatigue (77%), edema (72%), weight loss (27.7%), diarrhoea (11.11%), and shortness of breath (16.6%) were the presenting complaints. The kidney was the most commonly involved organ (55.6%), followed by the heart, nerves, gastrointestinal tract, and soft tissue [Table 1].

Predominant renal involvement: Out of the 18 cases, ten (55.6%) showed predominantly renal involvement. All instances were confirmed by kidney biopsy, which revealed amyloid deposits and Congo red positivity, and polarised light microscopy, which revealed apple green birefringence (Figure 1, 2). The most prevalent symptom was bilateral pedal edema and proteinuria in all ten instances. SFLC assay is available in 7 cases, with Lambda chain predominance noted in 6 cases and kappa chain in one. Bone marrow biopsy of all 10 cases showed plasma cells between 6-10%. ECHO was normal in all cases.

Predominant cardiac involvement: Out of the 18 patients, two (11.1%) showed predominantly cardiac involvement. Edema was observed in both cases, as was proteinuria in one. ECHO in both patients

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demonstrated signs of restrictive cardiomyopathy, with an MRI of the heart in both cases indicative of amyloidosis. SPEP showed a small M band in one case. Bone marrow biopsy of both cases showed plasmacytosis with plasma cells between 6-10%.

Predominant nerve involvement: Two (11.1%) of the 18 cases showed predominant neural involvement. Both cases presented with foot drop and proteinuria. SPEP showed an M band in both cases, which was <3g/dL. Bone marrow biopsy showed plasma cells of 6% in one case and 12 % in the other. Nerve conduction studies showed bilateral sensorimotor axonal neuropathy, abdominal fat pad aspiration showed amyloid deposits in one case, and ECHO was normal in both cases.

Predominant gastrointestinal tract involvement: Two (11.1%) out of 18 cases had predominant gastrointestinal tract involvement. Diarrhoea and intestinal obstruction were noted in one while bleeding per rectum in another. One case noted a gastro-jejunal junction nodule, while a colonoscopy revealed rectal nodularity. Histopathological analysis revealed amyloid deposits in both cases. ECHO was normal in both cases, while the SFLC ratio was altered in one case.

Predominant soft tissue involvement: Two (11.1%) of the 18 subjects showed major soft tissue involvement, with the tongue being the tissue involved. Both individuals had macroglossia, and a tongue biopsy revealed amyloid deposits. In both cases, proteinuria was observed. In addition, a bone marrow biopsy revealed 6-10% plasma cells.

Serum protein electrophoresis was done in all patients, and the M band was present in only 3 cases. The SFLC assay was performed on ten patients and was altered in nine cases (mainly in renal). In all 18 subjects, bone marrow biopsy revealed increased plasma cells. Amyloid deposits were present in one case. Four abdominal fat pad aspirations were made, and only one revealed an amyloid deposit

Table 1: Demographic data of the study

		No of cases	Percentage of cases
Age in years	30-40	1	5.5%
	41-50	6	33.5%
	51-60	9	50%
	61-70	1	5.5%
	>71	1	5.5%
Symptom	Fatigue	14	77%
	Edema	13	72%
	Loss of weight	5	27.7%
	Breathlessness	3	16.6%
	Diarrhoea	2	11.1%
	Bleeding manifestations	2	11.1%
Predominant organ involvement	Renal	10	55.6%
	Heart	2	11.1%
	Nerves	2	11.1%
	Gastrointestinal tract	2	11.1%
	Soft tissue	2	11.1%

DISCUSSION

Primary amyloidosis is caused by the deposition of monoclonal free light chains, which can occur either systemically from monoclonal gammopathy, multiple myeloma, or, less frequently, B-cell lymphoma, or locally from light chain synthesis. This most common type of amyloidosis results from plasma cell dyscrasia in which insoluble immunoglobulin light chain fragments are produced and polymerize into fibrils that deposit extracellularly, causing visceral organ dysfunction and death.[5,7]Amyloid deposits are mainly classified into localized or systemic forms. The subtypes of systemic amyloidosis include primary AL amyloidosis, secondary amyloid A (AA) amyloidosis, familial amyloidosis, and ß2-microglobulin related amyloidosis.[6]

In 1995, Kyle and Gertz conducted a retrospective analysis and reported on data from 474 cases of biopsy-confirmed AL amyloidosis. Ninety-nine percent of patients were older than 40 (median 64 years). Weight loss and fatigue were the prominent presenting complaint. We, too, noted similar findings. Less than one-tenth demonstrated macroglossia as compared to 11.1 % in our study.[9]

The study by Quock TP et al. aimed to estimate the incidence and prevalence of AL amyloidosis in the United States, using information from the Truven MarketScan Commercial and Medicare Supplement Databases from 2007 to 2015. The mean age was 63 ± 12 years, compared to 51.2 years in our study. As in our study, this study too found male predominance.[10]

From January 1, 1950, through December 31, 1989, records of those diagnosed with amyloidosis gathered from the Mayo Clinic were analysed. Twenty-one patients met the requirements for an AL diagnosis. There were 62% men and had a median age of 73.5 years. Although the median age is much higher than that of our study, concurrence was noted with gender prevalence.[11]

Dubrey et al. noted a male predominance and a mean age of 59 years in their analysis of 232 primary cardiac amyloidosis cases. Similar to our study, fatigue and weakness were the most common

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presenting symptoms with macroglossia in 12.5% of the individuals.[12]

Ahmed et al. examined 131 renal amyloidosis and found nephrotic syndrome followed by sub-nephrotic proteinuria as the frequent presenting complaint. A similar presentation was noted in our study too. The mean age was 45 ± 16.33 years, and 62.6% were males.[13]

Similarities in clinicopathological findings are noted in the study by Agarwal et al. Retrospective investigations and analyses of 40 cardiac amyloidosis patients were conducted. Twenty-six were males, and the median age at the presentation was 51 years. The most frequent presenting symptoms were weakness, exhaustion, and shortness of breath, with macroglossia noted in 10% of the patients.[14] Pinney et al., in their epidemiological study of systemic amyloidosis in England, noted that the incidence peaked at age 60–79 years, while we found 50 % of our cases in the 51–60-year group.[15]

Rajani et al. analysed 13 cases of peripheral nerve amyloidosis, ten males and 3 women made up this group of patients, with the median age being 61 years. Six individuals with neuropathy had sensory symptoms, two with motor symptoms, and five with mixed symptoms. In comparison, our study showed sensory motor involvement in 2 cases.[16]

Penner and Muller studied 15 cases of head and neck amyloidosis. There were 9 men and 6 women with an age range of 18–76 years (mean 55.7 years). In 8 of the 10 cases in which the tongue was involved, the primary complaint was macroglossia, as compared to 2 cases in our study.[17]

Qian et al. retrospectively reviewed peripheral nerve involvements in primary amyloidosis. Seven males and one female were noted with the age range of 52 to 66 years. Initial symptoms noted were symmetrical lower extremity numbness in 3 patients and lower extremity pain in 4. In the present study, foot drop was predominantly noted.[18]

Lachmann et al. studied 350 patients with presumptive AL amyloidosis. Hereditary amyloidosis was confirmed in 34 patients by genetic testing, eight of whom had concomitant low-grade monoclonal gammopathy of undetermined significance (24%), but in none of these patients' free light chains were identified in the urine. Circulating paraproteins were evident in the rest 273 patients with AL amyloidosis. In our study, Serum protein electrophoresis was done in all cases, and the M band was present in only three cases. SFLC assay was done in 10 cases and was altered in nine cases with predominant lambda light chain involvement similar to other studies.[19]

Organ involvement determines the clinical manifestation of AL amyloidosis, which is unpredictable and deceptive. Symptoms are frequently misdiagnosed and caught late. Insidious in nature, the presenting symptoms include both constitutional and systemic. Heart involvement occurs in 70–80% of patients, followed by kidney involvement in 50–60% of patients and 15-20% experience neuropathy. Three or more organs are implicated in 30% of patients. The kidney parenchyma is one of the most frequently involved sites in all systemic amyloidoses, including AL, AA, ALECT2, and several hereditary amyloidosis. Amyloidosis should be suspected in patients with non-diabetic nephrotic proteinuria, heart failure with preserved ejection fraction, non-diabetic neuropathy, or unexplained gastrointestinal symptoms/hepatomegaly.[5,20,21,22]

Due to the vagueness of symptoms, it is common for patients to have multiple evaluations, thereby delaying diagnosis. This significantly affects a patient's capacity to tolerate therapy and results in irreversible organ damage. Before overt heart failure and nephrotic syndrome manifest, cardiac and renal amyloidosis can be identified by NT-proBNP and albuminuria. Additionally, a monoclonal component can be identified at least 4 years prior to diagnosis. Therefore, by integrating biomarkers of organ involvement, haematologists can identify, diagnose, and treat patients during the presymptomatic period.[20,21,22]

A tissue biopsy is mandatory to ascertain the diagnosis of AL amyloidosis. Mass spectrometry proteomic-based analysis is the most reliable technique. A crucial component in determining heart involvement is an echocardiogram with strain imaging. When echocardiography results are unclear, cardiac magnetic resonance (CMR) imaging helps to identify heart involvement. Late gadolinium enhancement is the distinguishing characteristic of CMR in cardiac amyloidosis.[20,21,23]

In order to stop the further amyloid deposition and improve the likelihood of organ recovery in AL amyloidosis, the plasma cell clone's ability to produce amyloidogenic light chains must be eliminated, and the quantity of the implicated light chain in serum must be as low as possible. These treatments work well for AL amyloidosis.[22,24]

CONCLUSION

The results of this study demonstrate the clinicopathological features and underlying etiological causes of primary amyloidosis. Primary amyloidosis is an uncommon condition of the plasma cells that can manifest in a variegated way and proceed insidiously to organ failure. Therefore, early diagnosis and therapy is dependent on a thorough knowledge of clinical course of the disease and a high level of clinical suspicion.

Limitations of the study

The study's retrospective design did not allow for future testing. Immunohistochemistry and mass spectrometry were unavailable; therefore, we could not subtype the amyloid. For several cases, serum-free light chain assay research was not available.

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