(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 6, Page No: 1365-1372
November-December 2021

IJMSCR

Primary Amyloidosis - A Case Report

[1]Dr. R. Prasanna, [2]Dr. PA. Iswarya Shree Nee
[1]Postgraduate, [2]Post Intern,
[1]Department of General Medicine,
Kilpauk Medical College

***Corresponding Author:**
Dr. PA. Iswarya Shree Nee
MBBS, Govt Kilpauk Medical college

Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

Background:

A 52 years old female presented with complaints of bilateral swelling of legs, abdominal distention and facial puffiness for 20 days. On evaluation, we found a rare presentation of Primary AL amyloidosis.

Investigation:

In renal biopsy immunofluorescence study was done which revealed Lambda light chain positive on the glomeruli, Kappa light chain negative. Immunoglobulins and complement deposition were negative. In light microscopy acellular amorphous material was deposited in the mesangium and focally on the capillary loops which were PAS and silver negative and blue on trichrome stain. Congo red stain of renal biopsy showed material which was deposited in the mesangium and on the capillary loop on all glomeruli showed apple green birefringence under polarized light. Bone marrow aspiration was done twice and it was normal. Bone marrow biopsy was normal.

Conclusion:

Primary AL amyloidosis is a rare entity with incidence of 4.5 cases/ lakh. It is frequently caused by clonal expansion of bone marrow plasma cells that secrete monoclonal Ig LC depositing as amyloid in various tissues. Recent study shows that only in 20% of cases primary AL amyloidosis is not associated with bone marrow plasma cell proliferation as in this case while in the rest 70-80% of cases it is associated with plasma cell proliferation of bone marrow

Keywords: - Primary amyloidosis, AL amyloidosis, lambda light chain, kidney, normal bone marrow

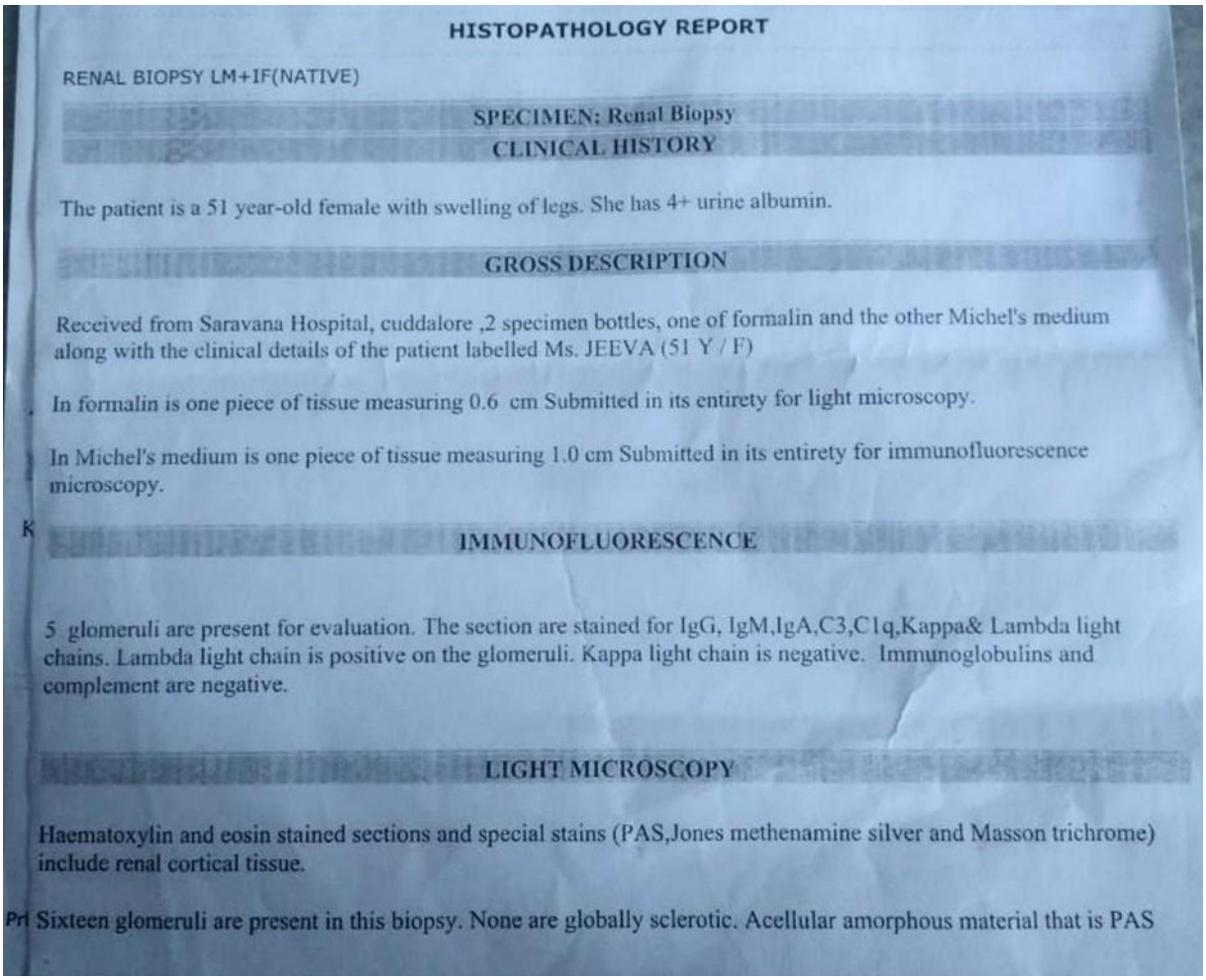
Introduction

Amyloidosis is a heterogeneous hereditary or acquired disease that results from abnormal deposition of beta-sheet fibrillar protein aggregates in various tissues. The most common type of amyloidosis is AL type. Kidney is the most common organ involved in systemic amyloidosis. Treatment mainly focuses on eradicating clonal plasma cell proliferation which produces amyloidogenic light chain. Here we discuss a rare case presentation of Primary AL amyloidosis.

Case History and Presentation

A 52 years old female presented with chief complaints of bilateral swelling of legs for the past 20 days upto the knee, not associated with any pain. This was followed by abdominal distention and facial puffiness for the past 15 days. No history of decreased urine output, fever or bleeding manifestation. No history of blood transfusion. At presentation, she was diagnosed with systemic hypertension. On examination, mild pallor and

bilateral pitting pedal edema were present. No lymphadenopathy. No organ enlargement. Investigations were done. Hemogram revealed mild anemia of 9.4g/dl with decreased packed cell volume of 31% and RBC count of 3.68million /cc. Peripheral smear showed normocytic normochromic anemia. Liver function test showed decreased total protein of 4.5g/dl and albumin level of 2g/dl. Serum calcium level was decreased around 9.5mg/dl. Urine routine revealed Albuminuria 4+ and Spot PCR was elevated around 6.97. ESR was elevated. Echocardiogram normal. Ultrasonography scan of the kidneys showed normal renal parenchymal echogenicity. Renal biopsy was done. In renal biopsy immunofluorescence study revealed Lambda light chain positive on the glomeruli, Kappa light chain negative. Immunoglobulins and complement deposition were negative. In light microscopy acellular amorphous material was deposited in the mesangium and focally on the capillary loops which was PAS and silver negative and blue on trichrome stain. Congo red stain of renal biopsy showed material which was deposited in the mesangium and on all glomeruli showed apple green birefringence under polarized light giving the impression of Amyloidosis AL type. Serum plasma electrophoresis revealed normal result. Bone marrow aspiration was done twice to rule out multiple myeloma which showed normal study with plasma cell count of 3%. Bone marrow biopsy was done and it showed normal histopathological study. Since there is extensive amyloid deposition in kidney and also since there is no evidence of bone marrow plasma cell proliferation or any lymphoproliferative disease the diagnosis of primary amyloidosis was made with no identifiable cause. After getting opinion from the hematologist the patient was started on Bortezomib, Lenalidomide, Dexamethasone, Antiplatelets and Antihypertensives. The patient is now on this treatment and is under regular follow up.



HISTOPATHOLOGY REPORT

RENAL BIOPSY LM+IF(NATIVE)

SPECIMEN: Renal Biopsy

CLINICAL HISTORY

The patient is a 51 year-old female with swelling of legs. She has 4+ urine albumin.

GROSS DESCRIPTION

Received from Saravana Hospital, cuddalore ,2 specimen bottles, one of formalin and the other Michel's medium along with the clinical details of the patient labelled Ms. JEEVA (51 Y / F)

In formalin is one piece of tissue measuring 0.6 cm Submitted in its entirety for light microscopy.

In Michel's medium is one piece of tissue measuring 1.0 cm Submitted in its entirety for immunofluorescence microscopy.

IMMUNOFLUORESCENCE

5 glomeruli are present for evaluation. The section are stained for IgG, IgM,IgA,C3,C1q,Kappa& Lambda light chains. Lambda light chain is positive on the glomeruli. Kappa light chain is negative. Immunoglobulins and complement are negative.

LIGHT MICROSCOPY

Haematoxylin and eosin stained sections and special stains (PAS,Jones methenamine silver and Masson trichrome) include renal cortical tissue.

Sixteen glomeruli are present in this biopsy. None are globally sclerotic. Acellular amorphous material that is PAS

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and silver negative and blue on trichrome stain is deposited in the mesangium and focally on the capillary loops in all glomeruli. This material is Congo red positive, giving apple green birefringence under polarised light.

There is no interstitial fibrosis and tubular atrophy. No proteinaceous casts are seen in the tubule.

Blood vessels are unremarkable.

DIAGNOSIS

Amyloidosis, AL type (see comment)

COMMENT

Kindly investigate for plasma cell dyscrasia

Bone Marrow Aspiration Report

Differential count:

Cell type	%
Blasts	00%
Promyelocytes	04%
Myelocytes	05%
Metamyelocytes	06%
Band and Neutrophil	34%
Eosinophil	04%
Basophil	00%
Lymphocyte	08%
Monocyte	01%
Plasma cells	03%
Erythroid series	35%

Number of cells counted :500

Cellularity –Normocellular marrow for age.

Myeloid- Erythroid ratio : 1.5:1

Erythropoiesis – Erythroid hyperplasia with Normal maturation. Morphology unremarkable

Granulopoiesis – Mildly decreased with Normal maturation.

(PTO)

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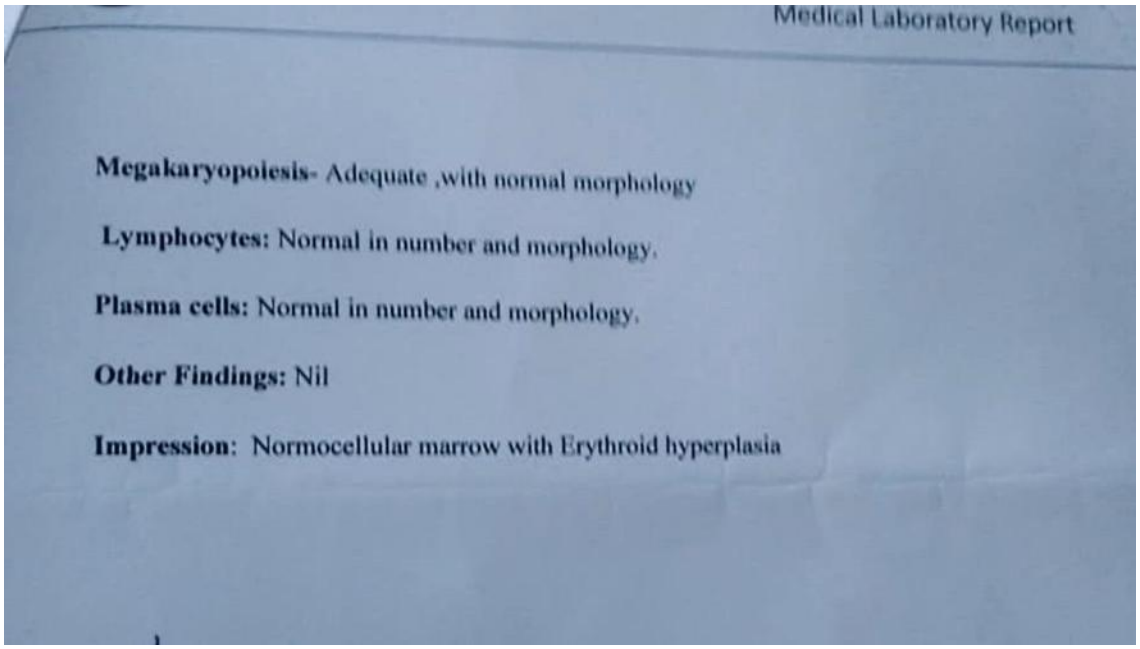

Medical Laboratory Report

Megakaryopoiesis- Adequate ,with normal morphology

Lymphocytes: Normal in number and morphology.

Plasma cells: Normal in number and morphology.

Other Findings: Nil

Impression: Normocellular marrow with Erythroid hyperplasia

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NAME OF THE PATIENT: JEEVA	AGE/SEX: 52/F	HOSPITAL ID(OP/IP): 3893/21	HPE NO: 6711/2021 ~~3842/2020~~ PS & BMA No. 434/21
REFERRED BY: CONTACT NO:		WARD/UNIT wd 141	~~IHC NO:~~
CLINICAL DIAGNOSIS: Renal Amyloidosis	PROCEDURE DONE: Bone Marrow Biopsy		DATE &TIME OF PROCEDURE: 14/9/2021 2.50 pm
NATURE OF SPECIMEN: Small Biopsy		SIDE: RIGHT/LEFT/BILATERAL –	DATE & TIME OF RECEIVING: 14/9/2021 3.10 pm
STATUS OF THE REPORT: Interim			DATE & TIME OF REPORTING: 16/9/2021 12pm.

METHODOLOGY: H&E /SPECIAL STAIN /IHC NO OF SLIDES : H&E____ /SPECIAL STAIN____/IHC____

~~GROSS DESCRIPTION:~~ PERIPHERAL SMEAR :-

RBC - Normocytic Normochromic RBCs.
No Anisopoikilocytosis. No nucleated RBCs.

WBC - Normal in count with following differential count
Neutrophils - 85%, Lymphocytes - 13%, Eosinophils - 2%.

Platelet - Adequate

Impression: Normocytic Normochromic RBCs with neutrophilic predominance.

~~MICROSCOPIC DESCRIPTION:~~

BONE MARROW ASPIRATION:

Cellularity – Cellular

Adequacy – Adequate

Myeloid : Erythroid – 3 : 1

Trilineage hematopoiesis – present

Erythroid series - Normal in count and morphology

(P.T.O)

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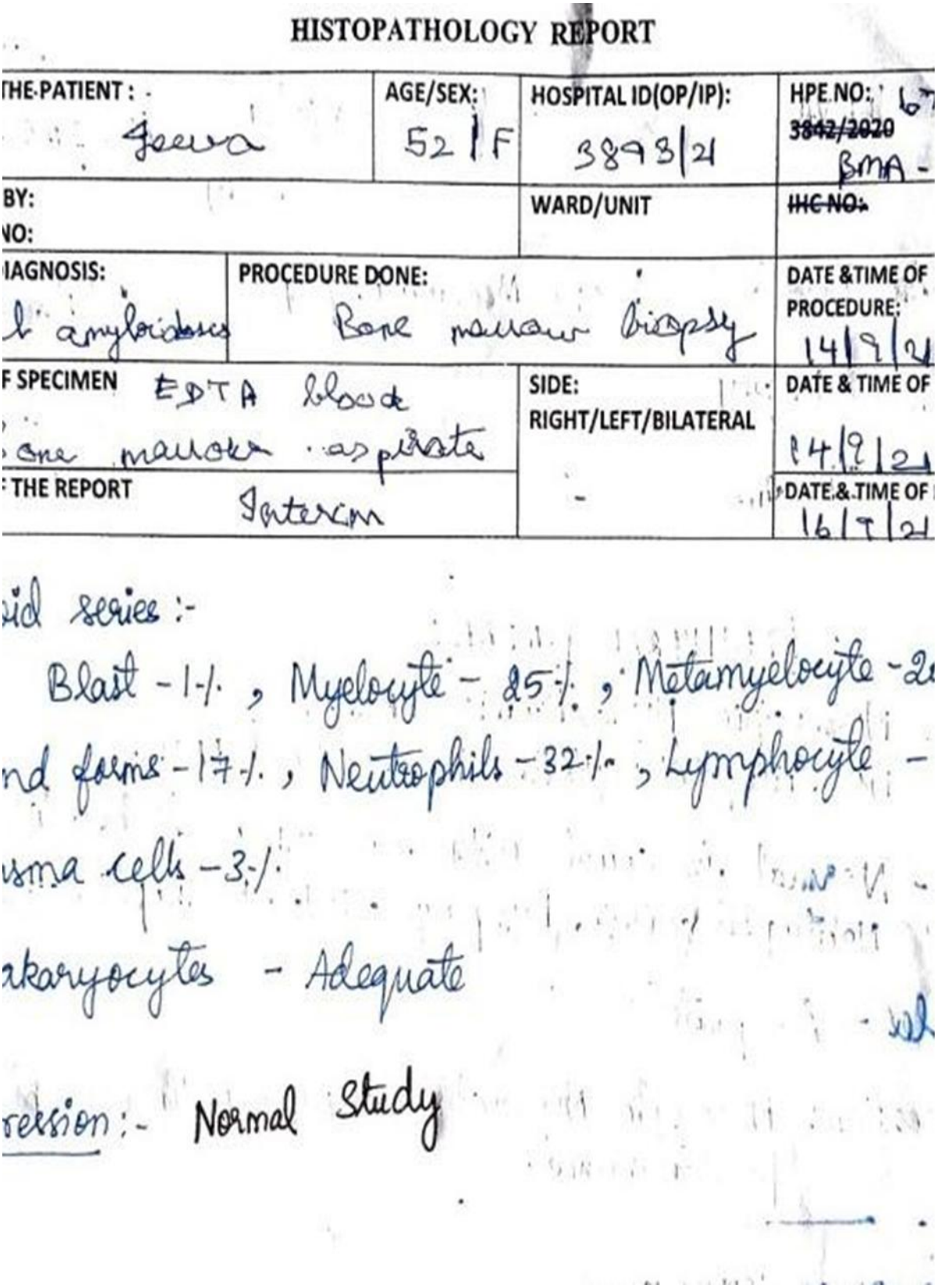

HISTOPATHOLOGY REPORT

THE PATIENT : Jeeva	AGE/SEX: 52 / F	HOSPITAL ID(OP/IP): 3893/21	HPE NO: 67 3842/2020 BMA -
BY: NO:		WARD/UNIT	IHC NO:
IAGNOSIS: l amyloidosis	PROCEDURE DONE: Bone marrow biopsy		DATE &TIME OF PROCEDURE: 14/9/21
F SPECIMEN EDTA blood one marrow aspirate		SIDE: RIGHT/LEFT/BILATERAL -	DATE & TIME OF 14/9/21
THE REPORT Interim			DATE & TIME OF 16/9/21

id series :-

Blast - 1-/. , Myelocyte - 25-/. , Metamyelocyte - 2
nd forms - 17-/. , Neutrophils - 32-/. , Lymphocyte -
sma cells - 3-/.

karyocytes - Adequate

ression :- Normal study

Discussion

Definition:

Amyloidosis consists of a diverse group of diseases characterized by misfolding of precursor protein, eventually forming highly ordered amyloid cross beta fibrils which deposit in various tissues. Amyloid aggregates can cause proteotoxic intracellular stress and direct cell damage leading to apoptosis. Amyloid fibril deposit disrupts tissue architecture, leading to

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progressive failure of organs. The disease can be localized or systemic.

Etiology:

The most common causes of amyloidosis are the immunoglobulin light chain related amyloidosis (AL), ATTR amyloidosis, and reactive amyloidosis (AA). AL amyloidosis is acquired and is caused by a small plasma cell clone that produces misfolded amyloidogenic light chains that deposits in various organs and tissues. AA amyloidosis is associated with various chronic inflammatory conditions, chronic or local microbial infections, rheumatoid arthritis and rarely with neoplasms. AL is the most common type of systemic amyloidosis.

Incidence:

AL amyloidosis has an incidence of 5-13 case per million person years. Familial transthyretin associated amyloidosis is a less common systemic type of amyloidosis. Men have higher incidence than women (1.3 fold) with the exception of secondary systemic amyloidosis for which female incidence was 1.9 times the male rate.

Pathophysiology:

Twentyone different proteins have been identified as amyloidogenic agents. Polypeptides can adopt alternative misfolded states, making them prone to aggregation. There are multiple processes by which misfolding of protein precursors occur. The protein may be intrinsically likely to acquire a pathological confirmation with aging, as seen in patients with wild type transthyretin senile systemic amyloidosis. This can also happen when there is high serum concentration of protein precursors, as seen in long term hemodialysis patients with increased levels of beta 2 microglobulin.

In hereditary amyloidosis, the replacement of single amino acids can lead to amyloidogenic misfolded proteins losing the biological function of the native Protein. In patients with AA amyloidosis, serum amyloid A, an acute phase reactant protein deposits in different tissues.

Histopathology:

One diagnostic and differentiating feature of amyloidosis is the apple-green birefringence of amyloid on congo red staining. Apart from this, amyloid has an amorphous eosinophilic appearance, when viewed with hematoxylin and eosin staining. On x ray diffraction analysis, it has a beta sheet structure.

Clinical Manifestations:

The most crucial factor for the diagnosis of amyloidosis is disease suspicion. Most symptoms are nonspecific, the diagnosis is often missed and delayed. Systemic amyloidosis (AA) can lead to heart failure with left ventricular hypertrophy on echocardiogram. Hepatomegaly, nephrotic syndrome, macroglossia, orthostatic hypotension, ecchymosis, autonomic and peripheral neuropathy can be present. Carpal tunnel syndrome, jaw claudication and articular deposits of amyloid can also be a manifestation of systemic amyloidosis. In secondary amyloidosis, hepatosplenomegaly, proteinuria, renal failure, and orthostasis can be seen. ATTR amyloidosis onset is during midlife and present with peripheral and autonomic neuropathy, cardiomyopathy and vitreous opacity. Amyloid beta amyloidosis is localized to the central nervous system and presents as sporadic Alzheimer's disease and aging.

Other findings that can lead to suspicion of amyloidosis are hypertrophied shoulder pads from amyloid deposition, amyloid purpura, and racoon eyes secondary to factor X deficiency in the case of AL amyloidosis.

Evaluation:

The diagnosis of AL amyloidosis should be considered in patients with unexplained proteinuria, cardiomyopathy, neuropathy, or hepatomegaly and in patients with multiple myeloma that has atypical manifestation.

The diagnosis of AL amyloidosis requires (1) demonstration of amyloid in tissue and (2) demonstration of a plasma cell dyscrasia. Tissue amyloid deposits demonstrate apple green birefringence when stained with congo red and viewed under polarized microscopy. Fine needle aspiration of abdominal fat is a simple procedure that is positive for amyloid deposits in >70% of patients with AL amyloidosis. Other tissues that allow for relatively non-invasive biopsy procedures are the minor salivary glands, gingiva, rectum, and skin.

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However, obtaining tissue from an affected organ may be necessary to establish the diagnosis of amyloidosis.

Once tissue diagnosis of amyloidosis has been established, demonstration of plasma cell dyscrasia by a bone marrow biopsy showing predominance of Kappa or Lambda producing plasma cells or by the presence of a monoclonal light chain in the serum or urine. In 70-80% of cases it is usually associated with plasma cell proliferation in bone marrow and in 20% of cases it is not associated with bone marrow involvement as in this case. Immunofixation electrophoresis should be performed on the serum and urine because, in contrast to multiple myeloma, the concentration of monoclonal light chain is often too low to be detected by simple protein electrophoresis.

Involvement of other organs have to be evaluated. For that cardiac function through ECHO, ECG, for kidney function evaluation of 24 hr urinary protein and eGFR are needed. Liver function tests and imaging can help with hepatic function assessment

Management:

The current therapeutic approach to systemic amyloidosis is based on the observation that organ dysfunction improves and survival increases if the synthesis of the amyloidosis protein precursor is halted. So, in AL amyloidosis the aim of therapy is to reduce rapidly the supply of amyloidogenic monoclonal light chain by supressing any plasma cell dyscrasia.

The association of an alkylating agent with high-dose dexamethasone has proven to be effective in two thirds of patients and is considered as the current reference treatment. New agents used in the treatment of multiple myeloma are under investigation and appear to increase hematological response rates. Several preliminary studies have shown encouraging results with novel anti-myeloma drugs such as thalidomide, lenalidomide and the proteasome inhibitor bortezomib. Combined with dexamethasone, these agents induce rapid haematological responses in most patients, even in those with refractory or relapsing disease. Bortezomib may also be combined with cyclophosphamide and dexamethasone with a good tolerance and impressive response rates. Bortezomib has to be used with caution in patients with advanced amyloid heart disease, who may occasionally develop abrupt reduction in left ventricular ejection fraction.

Symptomatic measures and supportive care is necessary in patients with organ failure. In selected cases, heart and kidney transplantation may be associated with prolonged patient and graft survival.

Prognosis:

Survival in AL amyloidosis depends on the spectrum of organ involvement (amyloid heart disease being the main prognosis factor), the severity of individual organs involved and haematological response to treatment. Prognosis is not influenced by the underlying plasma cell proliferation. However, identification of a neoplastic plasma cell population adversely affects survival, and a bone marrow plasma cell infiltration above 10% has been associated with poorer outcome. AL amyloidosis is a serious disease and causes death when treatment is delayed, whereas new therapeutic strategies induce haematological remission in most patients, with a median survival of more than 5 years. Early diagnosis is therefore a critical step in the care of these patients.

Conclusion:

So, primary AL amyloidosis need not necessarily be associated with bone marrow plasma cell proliferation or any lymphoproliferative disease. Rarely the reason may be due to occult plasma cell dyscrasias like extramedullary plasmacytoma.

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