EUROPEAN HEMATOLOGY ASSOCIATION

EHA-ISHBT Hematology Tutorial

Session 8: Plasma Cell Dyscrasia
Self-assessment Case 2

Speaker:

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Disclosures

- None

Introduction

- A 52 year old North Indian lady presented with 3 months history of
  - Swelling over feet & periorbital region
  - Exertional dyspnea (NYHA class II)
- Positive examination findings-
  - Periorbital edema
  - Pitting pedal edema
  - Raised jugular venous pressure
  - Hepatomegaly (Liver span 19 cm)
  - Splenomegaly (2 cm below the left costal margin)

Investigations

- Complete Blood Count
  - RBC- 3.6 × 10^{12}/l
  - Hb- 107 g/l
  - WBC- 10.8 × 10^{9}/l
  - Diff.- N 67%/L 25%/M 6%/ E 2%
  - Plts- 2.14 × 10^{9}/l
- Renal function tests
  - Urea- 15.5 mmol/l
  - Creatinine- 327umol/l
  - Uric acid 0.422 mmol/l
- Urine
  - 2+ proteinuria
  - No RBCs or pus cells
  - 24-hour urine protein- 1282 mg
- Liver function tests
  - Bilirubin 15.4 umol/l
  - AST- 32 U/L (15-46 U/L)
  - ALT- 61 U/L (13-45 U/L)
  - Alkaline phosphatase- 113 U/L (38-126 U/L)

Investigations

- Total protein- 45 g/l
  - Albumin- 22 g/l
  - Globulin- 23 g/l
- Serum Calcium- 1.87 mmol/l
- Sodium- 137 mmol/l
- Potassium- 3.9 mmol/l
- LDH- 237 U/L (126-240 U/L)
- Ultrasound abdomen
  - Liver- 19.6 cm
  - Spleen- 13 cm
  - Bilateral kidneys- echogenic, normal size, maintained corticomedullary differentiation

Investigations

- Kidney biopsy-
  - Amorphous eosinophilic deposits in glomeruli
  - PAS- weak
  - Congo red- positive
  - Immunofluorescence- Lambda positive

Investigations

- Serum protein electrophoresis & immunofixation- No M band
- Serum free light chains
  - Kappa LC- 48.82 mg/L
  - Lambda LC- 2733 mg/L
  - Ratio- 0.017
  - dFLC- 2684 mg/L
- Beta2 microglobulin- 5.108 mg/L

Investigations

- Bone marrow aspiration
  - 28% plasma cells
- Bone marrow biopsy-
  - Diffuse infiltration with plasma cells
  - IHC- Lambda restriction
- Myeloma FISH- negative for del17p; t(4;14); t(11;14); t(14;16)
- Skeletal survey (low dose CT)- no lytic lesions

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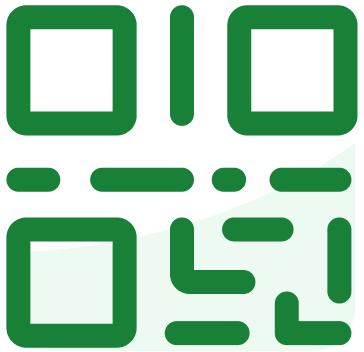

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Q1) What is most likely diagnosis?

1. Monoclonal gammopathy of renal significance
2. Multiple myeloma with AL Amyloidosis
3. AA Amyloidosis
4. Light chain deposition disease
5. Monoclonal gammopathy of undetermined significance with amyloidosis

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8.41 What is most likely diagnosis?

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Further workup

- 2D Echocardiography
  - Bi-atrial enlargement
  - Severe LV diastolic dysfunction (e/e’ = 28; E/A= 3.4)
  - Mild MR
  - Mild TR
  - IVC dilated
  - LV EF 55%

  - Impression- Restrictive cardiomyopathy

Further workup

- Cardiac MRI
  - Mild LV hypertrophy; Normal sized RV
  - Moderate bi-atrial enlargement

  - Delayed gadolinium enhancement shows suboptimal myocardial nulling
  - Diffuse subendocardial scar in basal, mid and distal LV segments not corresponding to coronary artery distribution
  - Focal scar along RV free wall

  - Impression- Infiltrative cardiomyopathy likely cardiac amyloidosis

Q2) Order of organ involvement in light chain amyloidosis?

1. Kidney>Heart>Liver>GI tract>Peripheral Nerves
2. Kidney>Heart>Soft tissue>Liver>Peripheral Nerves
3. Heart>Kidney> Soft tissue>Liver>Peripheral Nerves
4. Soft tissue>Heart>Kidney>Peripheral Nerves>Liver
5. Heart>Liver>Kidney>Peripheral Nerves>Bladder

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8.42 Order of organ involvement in light chain amyloidosis?

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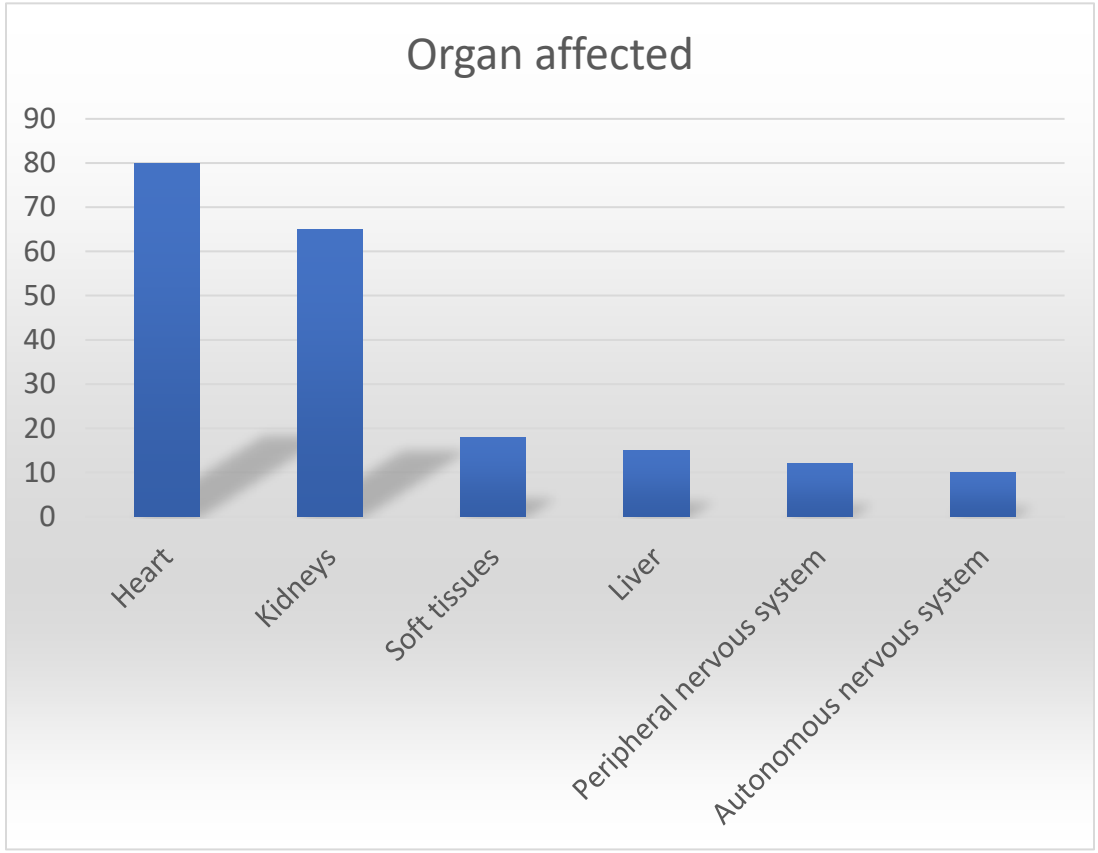
Organ involvement in amyloidosis

Type of Amyloidosis	Organ Involvement
AL Amyloidosis	Heart> Kidneys
AA Amyloidosis	Kidneys >>>Others
ATTR (transthyretin) Amyloidosis	Heart/ PNS >>>Others

Wechalekar AD, et al. Systemic amyloidosis. The Lancet. 2016 Jun;387(10038):2641–54.

Organ involvement in AL amyloidosis

- Cardiac involvement most common
- Maximum impact on prognosis
- Heart failure and proteinuria- may be confused with other common disorders



Merlini G, et al. Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers. 2018 Oct 25;4(1):38.

Q3) What further investigations would be advise for staging of this case?

1. Electrocardiogram, Troponin
2. Cardiac biopsy, Troponin
3. Troponin, Creatine kinase-MB
4. Troponin, N terminal pro BNP (Brain natriuretic peptide)
5. Electrocardiogram, Whole body PET CT scan

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8.43 What further investigations would be advise for staging of this case?

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AL Amyloidosis- Staging systems

Staging system	Troponin (ng/mL)	BNP (pg/mL)	Other	Stages
Mayo 2004	TnT ≥ 0.035	NT-pro BNP ≥ 332		I, II, III
European 2015 modification of Mayo 2004	TnT ≥ 0.035	NT-pro BNP ≥ 332	If Stage III- NT-pro BNP ≥ 8500	I, II, IIIA, IIIB
Revised Mayo 2012	TnT ≥ 0.025	NT-pro BNP ≥ 800	dFLC ≥ 180 mg/L	I, II, III, IV
Boston University 2019	TnT ≥ 0.1	BNP ≥ 81	If Stage III- BNP ≥ 700	I, II, III, IIIB

Al Hamed R, et al. Comprehensive Review of AL amyloidosis. Blood Cancer J. 2021 May 18;11(5):97.

Staging of our patient

- Kappa LC- 48.82 mg/L
- Lambda LC- 2733 mg/L
- Troponin T- 0.038 ng/mL
- NT-pro BNP- 3102 pg/mL

- Mayo 2004- Stage III
- European 2015- Stage IIIA
- Mayo 2012- Stage IV

Q4) Preferred choice for initial treatment for this patient?

1. Bortezomib/ lenalidomide/ dexamethasone
2. Carfilzomib/ lenalidomide/ dexamethasone
3. Daratumumab/ pomalidomide/ dexamethasone
4. Bortezomib/ cyclophosphamide/ dexamethasone
5. Daratumumab/ bortezomib/ cyclophosphamide/ dexamethasone

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8.44 Preferred choice for initial treatment for this patient?

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Treatment of AL Amyloidosis

- Anti plasma cell therapy

- Management of symptoms and organ toxicities
  - Heart failure, arrythmias
  - Fluid restriction, diuretics
  - Dialysis
  - Peripheral neuropathy

Treatment of AL Amyloidosis

- Anti plasma cell therapy
  - Efficacy against plasma cell clone
  - Toxicity (involving compromised organ)

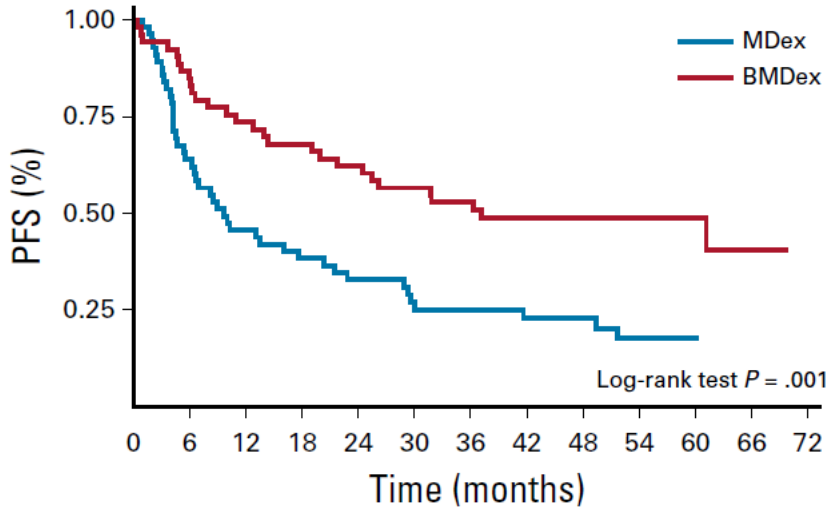
- Bortezomib + alkylating agent
  - Melphalan /dexamethsone (M/Dex) Vs Bortizimab(Bor)/MDex
  - Cyclophosphamide (Cy)BorDex

Treatment of AL Amyloidosis

- Mdex
  - Oral Melphalan 0.22 mg/kg/d X 4 days
  - Oral Dexamethasone 40 mg X 4 days

- BMDex
  - Bortezomib 1.3 mg/m^2
  - D 1, 4, 8, 11, for 2 cycles
  - D 1, 8, 15, 22 subsequently

- Any hematologic response after 3 cycles- 52% v/s 79% (p 0.002)
- VGPR or better- 29% v/s 55%



Kastritis E, et al. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. JCO. 2020 Oct 1;38(28):3252–60.

Treatment of AL Amyloidosis

- Bortezomib/cyclophosphamide/ dexamthasone (VCd or CyBorDex)
  - Bortezomib 1.3 mg/m^2 weekly
  - Cyclophosphamide 300 mg/m^2 weekly
  - Dexamethasone 40 mg weekly

Study	n	Stage III	ORR	Organ response	OS	TNT or PFS
Manwani *et al* 2019	915	51.3%	65%	Heart- 32.5% Kidney- 15.4%	Median OS 72 mo	Median TNT not reached at 7 y
Palladini *et al* 2015	230	49%	62%	Heart- 17% Kidney- 25%	5y OS 55%	Median PFS 13 months

Manwani R, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood. 2019
Palladini G, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in systemic AL amyloidosis. Blood. 2015

Treatment of AL Amyloidosis

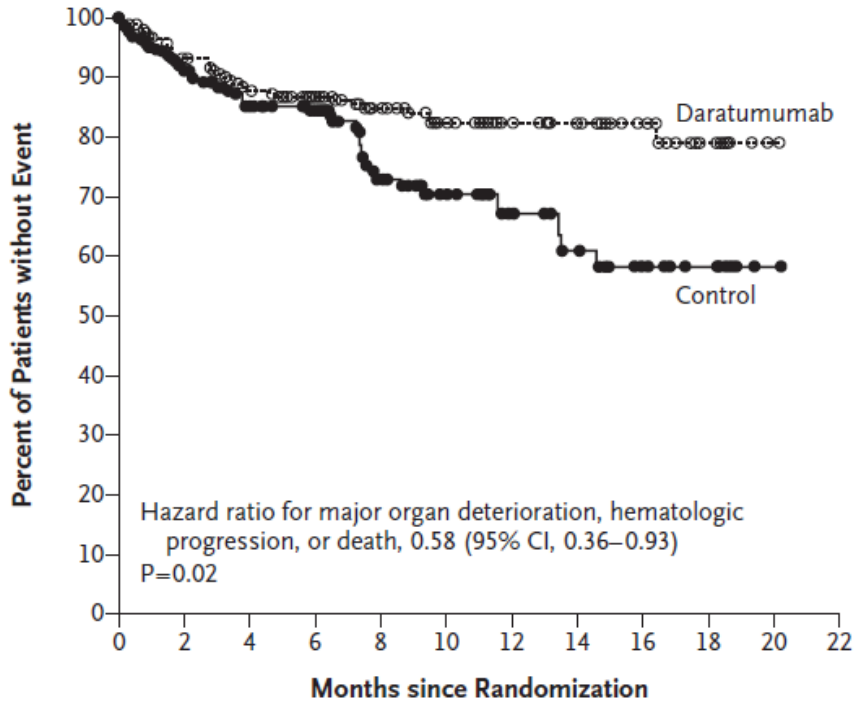
- ANDROMEDA trial
- CyBorDex vs Dara-CyBorDex
- Daratumumab 1800 mg SC
  - Weekly for first 2 cycles
  - Every 2 weeks cycles 3 to 6
  - Every 4 weeks till progression

Kastritis E, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021

Treatment of AL Amyloidosis

- ANDROMEDA trial- responses at 6 months

	DVCd	VCd
n	195	193
Complete hematological response	53.3%	18.1%
Cardiac response	41.5%	22.2%
Renal response	53%	23.9%



Kastritis E, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021

Treatment given to our patient

- Patient treated with
  - CyBorDex

- Treatment well tolerated
- Symptomatic improvement
  - Improved exercise tolerance
  - Fluid retention decreased

Treatment and response

- Response assessment after 4 cycles
  - Urea- 6.9mmol/l
  - Creatinine- 106 umol/l; eGFR- 47.2 mL/min/1.73 m^2

  - Kappa LC- 10.2 mg/L; Lambda LC- 45.6 mg/L
  - dFLC- 35.4 mg/L; Ratio- 0.22

  - NT-pro BNP- 722 pg/mL

  - 24 hour urine protein- 150 mg

Q5) What is the response status of our patient?

1. Complete hematological response with cardiac and renal response
2. Very good partial hematological response with cardiac and renal response
3. Complete hematological response with renal response, without cardiac response
4. Very good partial hematological response with renal response, without cardiac response
5. Partial hematological response with cardiac and renal response

Parameter	Baseline	After 4 cycles
Creatinine (umol/l)	327	106
eGFR (ml/m/1.73 m^2)	12.9	47.2
Proteinuria (mg/24 h)	1282	150
NT pro-BNP (pg/mL)	3102	722
FLC ratio	0.017	0.22
dFLC (mg/L)	2684	35

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8.45 What is the response status of our patient?

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Response assessment in AL Amyloidosis

Hematological response	Criteria
Complete response	Negative serum and urine IFE Normalisation of FLC
Very good partial response	dFLC <40 mg/L
Partial response	dFLC decrease by >50%
No response	Less than PR

Organ response	Criteria
Cardiac	NT-proBNP decrease by >30% or >300 ng/L (if baseline was >650 ng/L)
Renal	Proteinuria showing ≥ 30% decrease or drop to <0.5 g/24 hours in absence of worsening of eGFR
Hepatic	50% decrease in ALP or radiographic decrease in size of liver by ≥ 2 cm

Palladini G, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012

Q6) Which of these are NOT part of the eligibility criteria for autologous transplant in AL Amyloidosis?

1. Bone marrow plasmacytosis >10%
2. Age < 70 years; ECOG performance status < 2
3. NYHA Class < III; LVEF> 40%; Systolic BP≥ 90 mmHg
4. TnT < 0.06 ng/mL; NT-proBNP < 5000 ng/L
5. Diffusion capacity of the lungs for carbon monoxide(DLCO) > 50%

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8.46 Which of these are NOT part of the eligibility criteria for autologous transplant in AL Amyloidosis?

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Stem cell transplant in AL Amyloidosis

- EHA-ISA working group guidelines 2021
- Induction therapy prior to transplant recommended in all groups
- If CR/VGPR after initial treatment- transplant may be deferred to relapse
- Melphalan 200 mg/m^2; Lower doses with low eGFR
- Dialysis dependence not a contraindication
- If less than VGPR after transplant- next line of treatment

Sanchorawala V. Summary of the EHA-ISA Working Group Guidelines for High-dose Chemotherapy and Stem Cell Transplantation for Systemic AL Amyloidosis. HemaSphere. 2022

Further treatment of our patient

- Patient proceeded with Stem cell transplant
- G-CSF mobilisation
- Mel 200 conditioning
- No organ toxicities
- Post transplant- Bortezomib maintenance for 1 year- stopped in view of peripheral neuropathy
- Maintaining CR at 2 years

Summary and Take-home messages

- Suspecting AL Amyloidosis-
  - Cardiac- Restrictive cardiomyopathy with subendocardial thickening
  - Renal- Proteinuria; preserved renal size
- Diagnosing AL Amyloidosis
  - Tissue diagnosis; Congo red, Polarising microscopy
  - Typing of amyloid- Immunofluorescence; Mass spectrometry
- With or without large plasma cell clone
- Staging- Troponin T & NT pro-BNP
- Treatment- Dara-CyBorDex vs CyBorDex
- Autologous transplant- holds value

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Thank you