HOT NEWS

NELLE SINDROMI LINFOPROLIFERATIVE:
la storia continua

Waldenström Macroglobulinemia: a clinical case

Francesca Maria Quaglia, MD PhD
UOC Ematologia e CTMO AOUI Verona

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Disclosures of Francesca Maria Quaglia

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Astra Zeneca					x	x	
Janssen					x	x	x
Sandoz			x				
Amgen							x
Roche							x
Pfizer							x

Patient

- Male, dob 1940, **83 yrs**
- **Comorbidities:** ischemic-hypertensive heart disease (no major ischemic episodes, EF preserved), multi-district non-critical peripheral artery disease, arterial hypertension, hypertensive encephalopathy
- Allergy/Intolerances: aspirin (stomach pain, GE reflux)
- **Concomitant therapies:** clopidogrel 75 mg/d, statin interrupted due to normal cholesterol values, ramipril 2.5 mg/d

History

- **2017** (pt age 77 yrs)**:** MC IgMκ 7 g/L, no blood count alteration, no changes in hepato-renal function, no symptoms, no lymphadenopathy, no organomegaly → MGUS IgM, follow up
- **Feb 2020:** MC 8 g/L, *GE disconfort, constipation/diarrhea, weight loss (- 6 kg in 3 months), dizziness, paresthesia (feeling of cold feet)*
  - ✓ Gastroenterologist referral: bowel obstruction, gastroparesis? No specific causes, treated with probiotics
  - ✓ Neurologist referral: torpid osteo-tendon reflexes, lower limb apalesthesia: distal axonal peripheral sensory neuropathy

Figure-1. Diagnostic Approach to Suspected Waldenström Macroglobulinemia.

- Serum protein electrophoresis
- Serum immunofixation to validate the immunoglobulin M (IgM) heavy chain and the type of light chain
- Quantitative test for immunoglobulin G, immunoglobulin A, and IgM
- 24-hour urine collection for protein electrophoresis; monoclonal light chains are detected in the urine of 40%–80% of patients tested
- Immunoglobulin free light chain assay (long-term value not established)
- Serum β_2 microglobulin evaluation for prognosis; part of the international staging system for Waldenström macroglobulinemia
- Bone marrow biopsy; intertrabecular monoclonal lymphoplasmacytic infiltrate ranges from predominantly lymphocytic cells to overt plasma cells
- Cytogenetic studies with optional fluorescence in situ hybridization; *MYD88* mutational analysis required, *CXCR4* mutational analysis if MYD88 is mutated

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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

Gertz et al, 2021

AJH WILEY

- Computed tomography of abdomen and pelvis to detect organomegaly and lymphadenopathy (a skeletal survey and radiographic imaging of the bones are unnecessary in the absence of symptoms; lytic bone lesions are unusual)
- Serum viscosity required when signs and symptoms of hyperviscosity syndrome are present or when IgM >4000 mg/dL
- Ophthalmologic evaluation for hyperviscosity
- On the basis of clinical presentation, analysis involves Coombs test (cold autoantibody) and cryoglobulin or tissue stains for amyloid deposits
- Of myeloma patients, 1% have IgM, and their disorder behaves like other multiple myeloma[42]
- Hepatitis B and C screening is necessary if rituximab therapy is planned

Optional (if clinically indicated)

- Cryoglobulins
- Cold agglutinin titre
- Serum viscosity
- Screening for acquired von Willebrand disease
- 24-h urine protein quantification
- Serum FLCs
- NTproBNP, cardiac troponins
- EMG, anti-MAG, anti-GM1 (consultation with neurologist)

[a]Fever, night sweats and weight loss.
anti-GM1, anti-ganglioside M1; anti-MAG, myelin-associated globulin antibody; B2M, β2 microglobulin; BM, bone marrow; CT, computed tomography; EMG, electromyogram; FLC, free light chain; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IHC, immunohistochemistry; Ig, immunoglobulin; NTproBNP, N-terminal pro b-type natriuretic peptide; WM, Waldenström's macroglobulinaemia.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

CLINICAL PRACTICE GUIDELINES

Annals of Oncology 29 (Supplement 4): iv41–iv50, 2018
doi:10.1093/annonc/mdy146
Published online 5 July 2018

Kastritis et al, 2018

Amyloidosis?

- **Sept 2020:** Hb 12 (13.5-16) g/L; MC IgMκ 9.3 g/L, normal FLC, BJ negative

- Myocardial scintigraphy/US: no alterations
- Spinal MRI: lumbar disc disease, osteoarthritis of the spine
- Due to the Covid-19 pandemic: no regular check-up, bone biopsy/periumbilical fat biopsy not done

- Pregabalin 50 mg with mild symptom relief

Recent history

- **March 2023 (83 yrs):** *worsening of paresthesias*, evening fever (37.8°C) without any sings of infection, MC IgMκ 13.9 g/L, IgM 18 g/L, IgA 0.3; IgG 8 g/L, BJ 29 mg/L, albumin 36 g/L, LDH 137 U/L; no cryoglobulins, no lymphadenopathy, no organomegaly
- **BM biopsy**
  - ✓ Predominantly small lymphocytes CD20, CD79a, CD25+, in IgM kappa + also in the form of plasma cells (infiltration 70%)
  - ✓ The search for amyloid substance with **Congo Red** staining was **negative**
  - ✓ Diffuse pattern lymphoid infiltrate with IgM kappa secretory component suggesting a lymphoproliferative process with secretory differentiation, compatible with **lymphoplasmacytic lymphoma** in the appropriate clinical-laboratory context

International Prognostic Scoring System for Waldenström macroglobulinemia

- Age 83 yrs, Hb 11.2 g/L, PLT 350x10^9/L, β2m 2.7 mg/L, MC IgMκ 13.9 g/L → IPSSWM Intermediate
- anti-MAG detection: negative
- proBNP, Tp, albumin, LDH: within normal range

Gertz et al, 2021

Factor Associated With Prognosis		Value
Age, y		>65
Hemoglobin, g/dL		≤11.5
Platelet count, No./mcL		≤100 000
β_2-Microglobulin, mg/L		>3
Monoclonal IgM, g/dL		>7
Risk Stratum and Survival		
Risk Category	**Score[a]**	**Median Survival, mo**
Low	0 or 1 (except age)	142.5
Intermediate	2 or age > 65 y	98.6
High	>2	43.5

Note: Adapted from Morel et al[55] Used with permission.
Abbreviation: IgM, immunoglobulin M.
[a]One point is assigned for each positive factor and the risk score is the sum of points.

Table 3. Indications for initiation of therapy in patients with WM [31]

Clinical indications for initiation of therapy

- Recurrent fever, night sweats, weight loss, fatigue
- Hyperviscosity
- Lymphadenopathy: either symptomatic or bulky (≥ 5 cm in maximum diameter)
- Symptomatic hepatomegaly and/or splenomegaly
- Symptomatic organomegaly and/or organ or tissue infiltration
- Peripheral neuropathy due to WM

Laboratory indications for initiation of therapy

- Symptomatic cryoglobulinaemia
- Symptomatic cold agglutinin anaemia
- Autoimmune haemolytic anaemia and/or thrombocytopaenia
- Nephropathy-related to WM
- Amyloidosis-related to WM
- Hb ≤ 10 g/dL
- Platelets < 100×10^9/L
- IgM levels > 60 g/L

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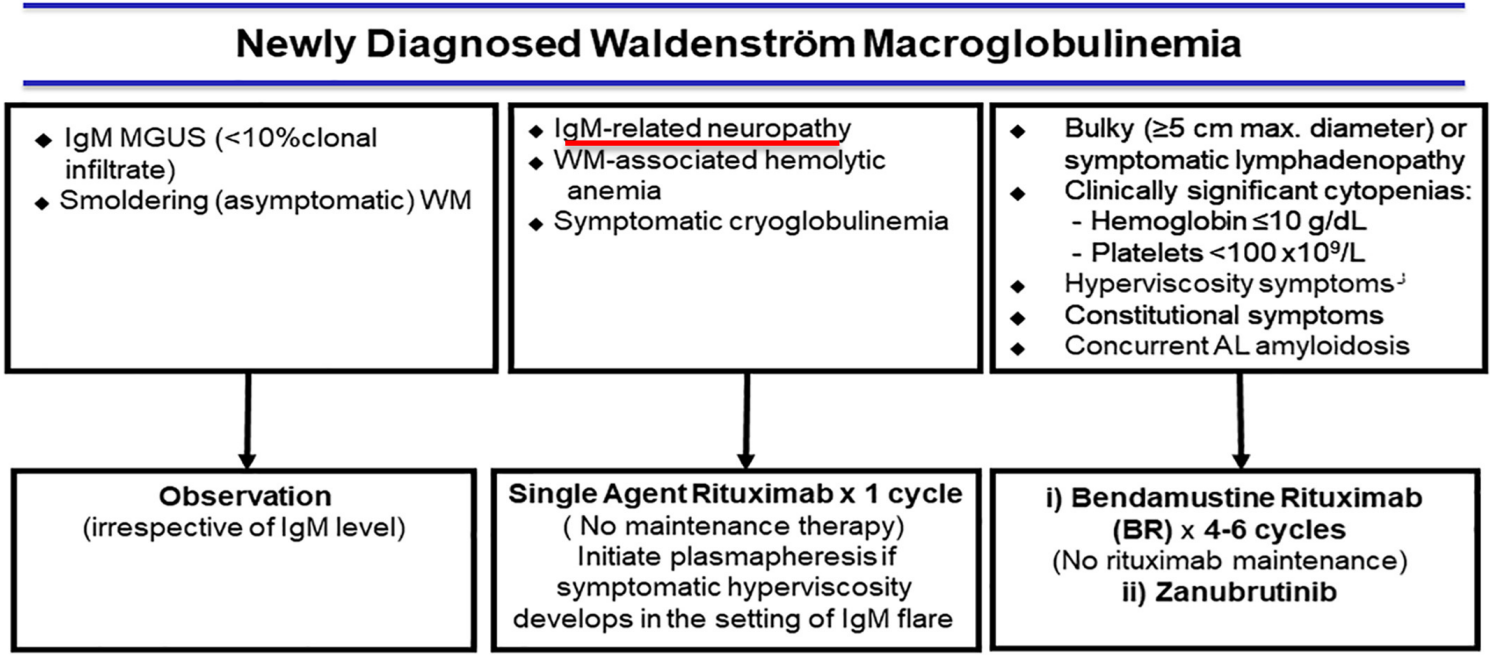
CLINICAL PRACTICE GUIDELINES

Kastritis et al, 2018

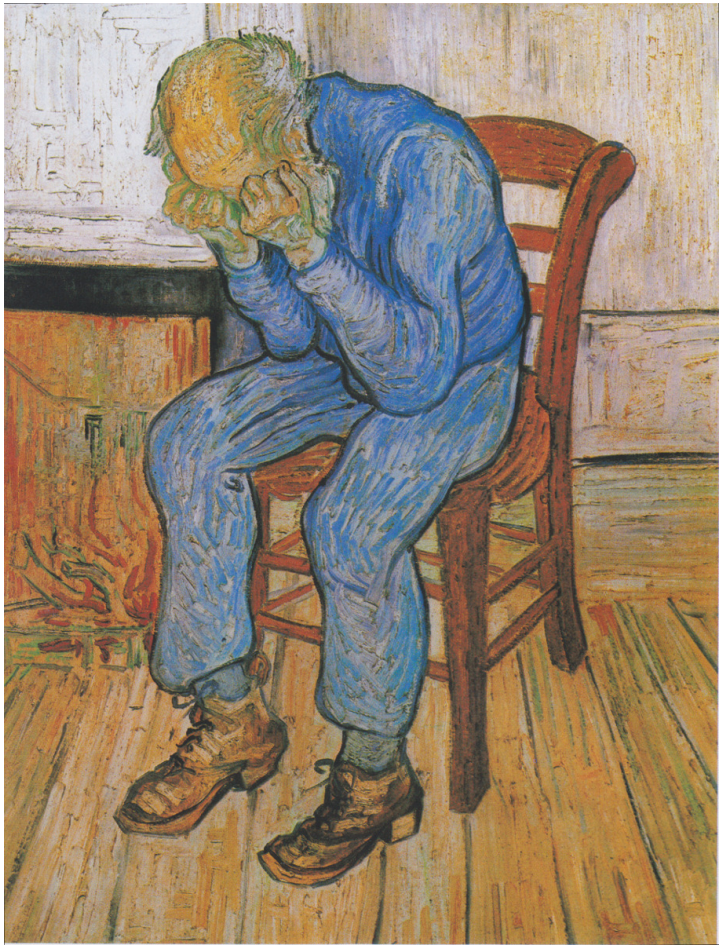
Treatment of specific WM-related conditions
- WM-related amyloidosis
- WM-related peripheral neuropathy
- Bing-Neel syndrome

Upfront treatment of WM

Mayo Clinic mSMART guidelines



Gertz MA et al, *JCO*, 2022



- **Management of peripheral neuropathy associated with IgM monoclonal protein remains frustrating for clinicians**
- Mechanism of neuropathy is thought to be demyelination due to direct binding of antibody to myelin-associated glycoprotein
- Treatment of IgM-associated peripheral neuropathy can be similar to that of WM; **Rituximab monotherapy retains a relevant role**

  In a double blind, placebo-controlled trial, 54 pts with anti-MAG IgM chronic demyelinating neuropathy were randomized to placebo or rituximab. The primary outcome of absolute improvement in ISS (INCAT sensory score) from baseline at 12 months was not achieved as no significant difference in the change in ISS was seen between rituximab and placebo groups
- **Therapy of IgM associated neuropathy remains inadequate**

Gertz et al, 2021; Gruson et al, 2011; Leger et al, 2013

Which therapeutic approach?

- Rituximab monotherapy?
- Other?

Our choice

- **Zanubrutinib 80 mg x 2/d (8 May 2023)**
- ECOG 1-2, Hb 11 g/dl, plts 315.000/mmc, GB 6800/mmc, N 3160/mmc, normal renal and hepatic function, normal level of LDH

Tam CS et al, *Blood*, 2020 the ASPEN study

End points/AEs

- 24 May 2023: ***marked improvement in neurological symptoms***
- Hb 11.3 g/dL, GB 7150/mmc, N 2970/mmc, L 3310/mmc, MCV 93.8, PLT 242000/mmc

- ….but *bleeding at home*: bruising, hematomas in the upper limbs, rectal bleeding possibly due to hemorrhoidal bleeding
- He stopped clopidogrel → the bleeding episodes resolved

Concomitant drug management

- Cardiological referral to reevaluate clopidogrel therapy and substitution with another drug, possibly at a lower dose, if necessary to maintain the antiplatelet prophylaxis, in consideration of the risk of bleeding linked to zanubrutinib: stop clopidogrel, no other drug

BTKi dose

- Zanubrutinib at the same dosage…

➢ Although data about dose reduction are increasing, they can result contradictory and inhomogeneous across pathologies. Moreover, current understanding of the impact of BTKi dose reduction on clinical effectiveness is conflicting and potentially dependent on disease characteristics

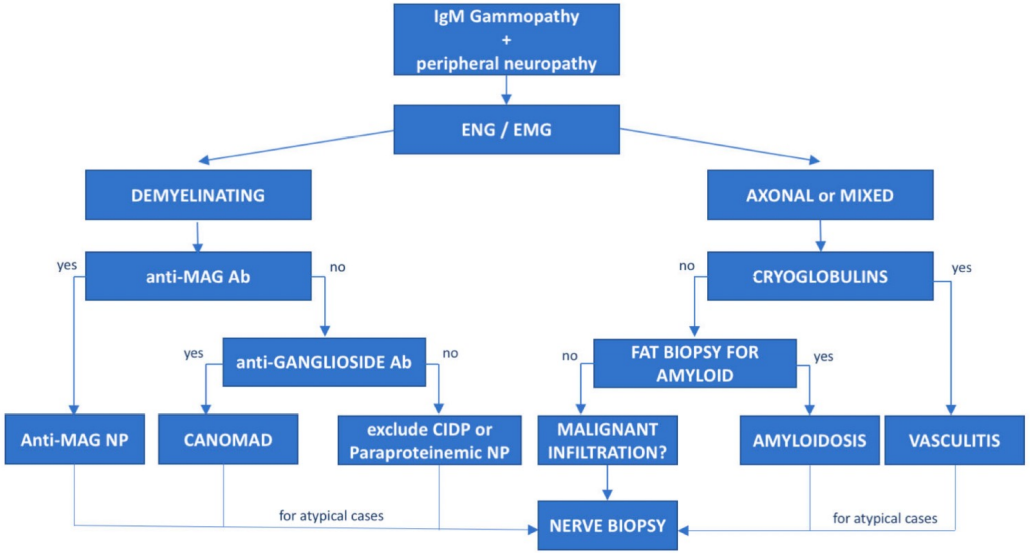
Sarosiek et al, 2023; Tohidi-Esfahani et al, 2023

Comment

- This patient illustrates non common features of the disease: extramedullary involvement at initial diagnosis with symptomatic presentation, late diagnostic tests, early response of the neuropathy with zanubrutinib

Gertz et al, 2021, Cao et al, 2015

WM-related neuropathies



DISEASES		TREATMENTS
Anti-MAG antibody neuropathy	IgM MGUS	Rituximab
	CLL	Obinutuzumab BTKis or venetoclax ± rituximab
	WM/MZL	Rituximab ± chemotherapy BTKis or venetoclax
Paraproteinemic neuropathy (anti-MAG antibody negative) Cryoglobulinemia	IgM MGUS	Rituximab
	CLL/WM/MZL	Rituximab ± chemotherapy ± bortezomib BTKis or venetoclax
POEMS syndrome AL amyloidosis	IgG or IgA MGUS	Bortezomib Lenalidomide
	IgG or IgA MM	Daratumumab ± bortezomib ± IMIDs Autologous stem cell transplant
Castleman's diseases		Siltuximab
Intravascular lymphoma neurolymphomatosis		Rituximab-based chemotherapy

MYD88^{L265P} variant has a high prevalence (66.7%) in anti-MAG antibody neuropathy

Visentin A et al, *Cells*, 2022

Closing remarks

- Earlier BOM…
- Fat biopsy
- Anti-GM1
- **Longer follow up**

Gertz et al, 2021; Kastritis et al, 2018

Thank you for your attention