Indian Journal of
Neurology

Open Science Publications

Volume 6, Issue 1 - 2025

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Waldenstorm's Macroglobulinemia: The Great Masquerader: A case Report

Case Report

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Article Information: **Submission:** 18/05/2025; **Accepted:** 09/06/2025; **Published:** 10/06/2025

Abstract

Waldenström's Macroglobulinemia (WM) is a slow growing hematological malignancy characterized by proliferation of plasma cells, lymphocytes and plasmacytoid lymphocytes in bone marrow secreting monoclonal immunoglobulin IgM and a risk of hyper viscosity syndrome. This case report highlights a unique presentation observed in a 60 years old farmer with neuropathy, and necrotizing soft tissue infection as the primary manifestation of WM. Notably, our patient had recurrent spontaneous hemolysis and presented to us a second time withAcrocyanosis, prompting for evaluation of cold agglutinin disease.This led to the final diagnosis of WM. Treatment was commenced with Bendamustine, Rituximab and Dexamethasone led to complete response (normalization of serum IgM and absence of bone marrow and extramedullary disease). As of the publication of this report, patient is in remission. In our case the patient had manifestations of symmetric peripheral neuropathy which predated all other manifestations, evaluation for the same might have prevented the potentially life-threatening necrotising infection he subsequently presented with.

Keywords: Waldenstorm's Macroglobulinemia; Cold Agglutinins; Peripheral Neuropathy; Necrotising Soft Tissue Infection; Autoimmune HaemolyticAnaemia; ImmunoglobulinM Monoclonal Gammopathy

Patient Description

Case of a previously healthy 60-year-old farmer in Odisha presented with swelling, redness and local rise of temperature of distal extremities of upper and lower limbs to SCB MCH, Cuttack during the month of December. A month prior he had started developing complaints of distal symmetric paranesthesia (numbness and pins and needle sensation) in his upper and lower limbs, which was unprovoked and constant for which and he had not sought medical care.Two weeks prior seeking medical care he had a spontaneous painless ulceration over his scrotum. At presentation the ulcer had a clear base and margins appeared gangrenous. This was not associated with fever, prior history of insect bite, discharge per urethra. Over the course of a week he then developed fever and was treated at a local hospital for which he received empirical antibiotics.The following week he suddenly developed swelling and erythematous discoloration of his hands and feet which prompted him to seek medical care in our hospital.

Provisional Diagnosis

He had no prior medical or family history or toxin exposure. Within a day following admission the discolouration had rapidly spread to extend into mid- forearms and mid-calf. Prompt arterial and venous doppler was done which showed patent vessels with normal flow, however muscular plains showed soft tissue oedema and heterogeneous density, a provisional diagnosis of necrotising soft tissue infection was made and empirical antibiotics was initiated with Intravenous (IV) Vancomycin, IV Meropenem and

IV Clindamycin.Creatinine Phosphokinase (CPK) was 63,100 mg/dl and Myonecrosis was confirmed via MRI. Bone marrow aspiration showed lymphoplasmatic cells and plasma cells constituting 20% of all Mononuclear cells.

Multiple Myeloma thus was ruled out due to absence of greater than 60% clonal plasma cells and absence of myeloma defining events, and light chains Serum involved / uninvolved<100. Bedside blood samples collected post admission underwent recurrent spontaneous hemolysis and thus under suspicion of cryoglobulinemia, DCT- ICT was sent: DCT positive [4+] for cold agglutinins {titre>1:1024}.

Due to the constellation of presentations of neuropathy, ulceration and Necrotising soft tissue infection (NSTI) and cold agglutination a provisional diagnosis of secondary Cold agglutination disease, secondary to lymphoproliferative disorders, monoclonal gammopathyor autoimmune disorders was considered.

Evaluation and Investigations

Bed-side evaluation showed a discreet solitary inguinal lymphadenopathy which was however not amenable for biopsy, USG showed, hepato- splenomegaly and multiple enlarged peri pancreatic and para-portal lymph nodes, which were aspirated and had evidence of reactive hyperplasia. Serum electrophoresis was negative for M band, however increased kappa light chains 354.28mg/L[3.30mg/L-19.40 mg/L] tested on SPAplus software. K/l ratio: 9.87 seen on immunofixation. In addition, viral marker for HCV was negative (Table 2), Swab culture from scrotal ulceration was sterile, peripheral blood sample drawn prior commencement of antibiotic was sterile, Serum Procalcitonin was negative, and Bone marrow aspiration showed erythroid hyperplasia with lymphoplasmacytic cells consisting of 20% of mononuclear cells.

Despite resolution of symptoms there was persistent motor weakness. Nerve conduction study (NCS) showed evidence of motor-sensory axonal demyelinating neuropathy of all limbs. There was gradual response to antibiotic regimen with reduction of inflammation and over the course of two weeks. Over the course of a month the patient had improved with no constitutional symptoms however had persistent motor weakness in distal extremities and was

Table 1: Free Light Chain Ratio First Consultation

TEST NAME	Result	Units	Biological Reference Interval
Kappa, Free light chain	260.05	Mg/L	3.30-19.40
Lambda, Free light chain	26.7	Mg/L	5.71-26.30
Kappa/Lambda ratio	10.03	-	0.26-1.65
Beta-2 Microglobulin, SERUM	-	Mg/L	0.80-2.34

Table 2: Free Light Chain ratio (sample 2) on re-vist with revision of diagnosis.

TEST NAME	Result	Units	Biological Reference Interval
Kappa, Free light chain	260.05	Mg/L	3.30-19.40
Lambda, Free light chain	26.7	Mg/L	5.71-26.30
Kappa/Lambda ratio	10.03	-	0.26-1.65
Beta-2 Microglobulin, SERUM	-	Mg/L	0.80-2.34

Table 3: Immunohistology work up: Direct Agglutination Test

POLYSPECIFIC C3D&IgG	(+)2
MONOSPECIFIC C3d	(+)2
MONOSPECIFIC IgG	Negative
AUTOCONTROL	
4 degree Celsius	(+)2
Room Temperature	Negative
37 degree Celsius	Negative

Suggestive of COLD Autoimmune Haemolytic Anemia

Table 4: Immunocytochemistry Of Bone Marrow Aspirate

mmunocytochemistry	
CD3 (paracortical area)	POSITIVE
Bcl2(Interfollicular cells)	POSITIVE
CD20(germinal centre cells)	POSITIVE
CD5	POSITIVE
Ki67	LOW
CD10	NEGATIVE
Bcl6	NEGATIVE
CD23	NEGATIVE

Table 5: Sensory Nerve Conduction Study; 15 Days Post Admission During Primary Visit

SENSORY NERVE STUDY(SNS): UPPER LIMB; MEDIAN AND ULNAR NERVE				
SITE	**Latency (ms)**	**Duartion (ms)**	**Amplitude (microV)**	**NCV(m/s)**
RIGHT WRIST MEDIAN	2.96	2.04	40.9	43.92
LEFT WRIST MEDIAN	2.88	2.17	51.4	45.14
RIGHT WRIST ULNAR	2.67	3.08	46.3	4.94
LEFT WRIST ULNAR	2.46	2	49	48.78
LOWER LIMB: NO RECORDING				
RIGHT MID CALF				
LEFT MID CALF				

Impression : Normal Sns In Upper Limb With No Recording In Lower Limb:

Table 6: Nerve Conduction Study: Motor Nerves
15 days post admission during primary visit

	Latency (ms)	Duration (ms)	Amplitude (mV)	NCV (m/s)
Rt WRIST MEDIAN	4.90	20.73	3.0	
ELBOW	10.52	21.25	2.0	44.48
Lt WRIST MEDIAN	5.10	13.96	5.1	
ELBOW	10.43	13.96	4.6	46.99
RT WRIST ULNAR	2.60	15.10	10.7	
ELBOW	8.65	14.69	9.2	44.63
Lt WRIST ULNAR	2.92	13.13	9.3	
ELBOW	8.85	13.85	8.6	45.53

LOWER LIMB: NO RECORDING IN BILATERAL POSTERIOR TIBIAL NERVE AND COMMON PERONEAL NERVE

IMPRESSION: Increased distal latency, decreased CMAP, decreased nerve conduction velocity in bilateral median nerve with normal duration; Normal distal latency, duration, CMAP with decreased Nerve conduction velocity (NCV) in bilateral ulnar nerve. NO recording in bilateral posterior Tibial and common personal nerves.

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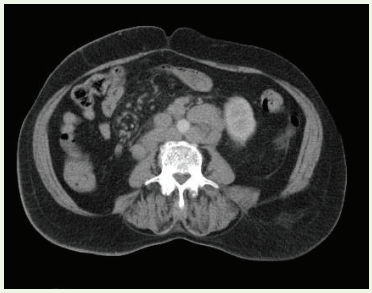


Figure 1: Axial section of CECT abdomen in portal venous phase showing multiple enlarged homogenous pre-aortic, para-aortic and aortocaval, perivcaval and retrocaval nodes.

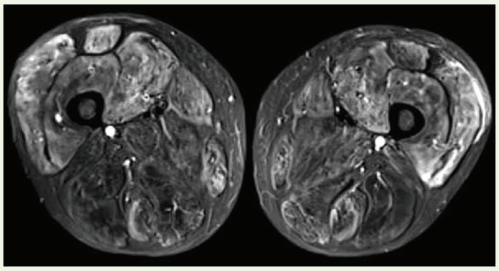


Figure 2: STIR images showing inhomogenous increased signal intensity of visualised thigh muscles

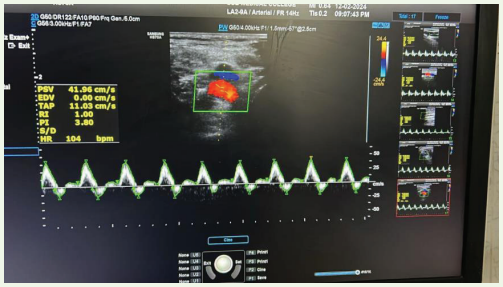


Figure 3: Peripheral arterial spectral study showing normal multiphasic flow

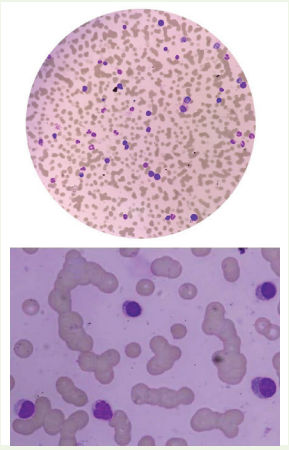
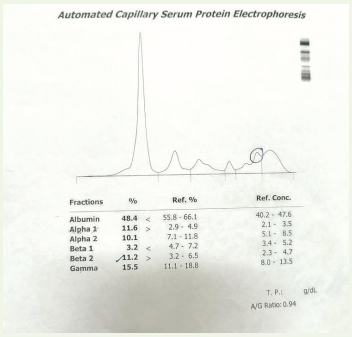


Figure 4: Bone marrow aspiration study showing lymphoplasmacytic cells constituting 20% of mono-nuclear cells



Report 5: SERUM PROTEIN ELECTROPHORESIS: showing M spike

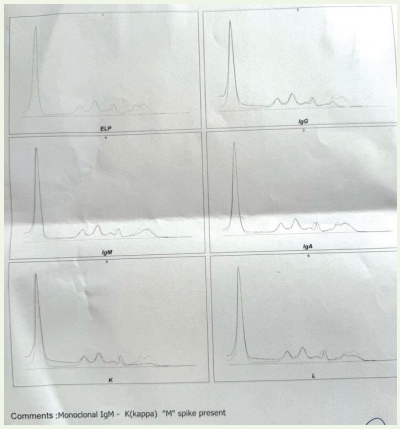


Figure 6: IMMUNO-FIXATION SHOWING: IgM; Kappa spike present

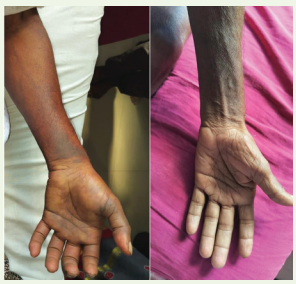


Figure 7: LEFT UPPER LIMB PRE AND POST DISCHARGE (Left) day 1 of admission; (Right) day of discharge

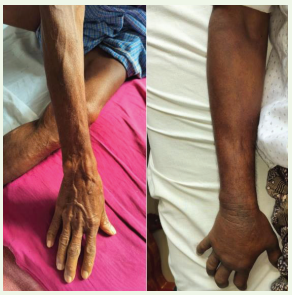


Figure 8: RIGHT UPPER LIMB PRE AND POST DISCHARGE (Left) day 1 of admission; (Right) day of discharge

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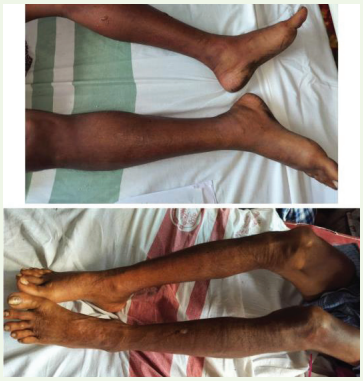

Figure 9 : Lower limbs pre and post discharge: (left) pre discharge, (right) post discharge

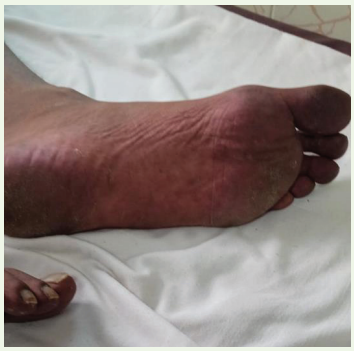

Figure 10: Acrocyanosis as reported a week after discharge.

ambulatory with support. At this stage he was discharged on request and advised follow up at two weeks with and to review sos.

Provisional diagnosis of lymphoma vs primary CAD

A week following discharge he had complaints of painless persistent erythema of dorsum of bilateral feet, and hands, and had sought tele -consultation. Features were suggestive of acrocyanosis; refusing admission patient presented to follow up after a month.

He showed progressive thrombocytopenia in serial CBC; at this stage he presented with a fresh attack of acrocyanosis and cold AIHA was confirmed. Repeat electrophoresis showed presence of m-spike with increase in k/l ratio 10.03; kappa light chain 268.03mg/L [3.30mg/L -19.40 mg/L] tested on SPA plus. Follow up of lymph node examination showed increase in size in the inguinal node. Excision biopsy of inguinal lymphnode was suggestive of non-Hodgkin lymphoma.

Treatment

Adiagnosis low grade lymphoma with secondary CAD was done at this stage and a cycle of BR [Bedamustine-Rituximab] was commenced. A month later on followup are peat electrophoresis showed 214.73[3.30mg/L -19.40 mg/L] tested on SPA plus: K/L ratio 14.56 (rising trend) M-spike present with IgM component. Repeat bone marrow aspiration showed presence of lymphoplasmacytic cells; plasma cells >10%.

Diagnosis was revised to WM and patient was commenced on BRD regimen and after 6 cycles of therapy is currently in remission with no symptoms of hyper viscosity subsequent to initiation of treatment.

Follow-up and outcomes

As of the publication of this report, patient is in remission. His neurological defect has sufficiently recovered that he is now ambulatory with support of a walking stick. No further complications were encountered during treatment duration or subsequently thereafter.

Discussion

Waldenstorm's macroglobulinemia (WM) or lymphoplasmacytic leukemia is a rare hematological malignancy and poses a challenging diagnosis due to lack of specific immunopathology. The diagnostic criteria of thedisease are:

1. Presence of IgM monoclonal gammopathy of any size
2. Greaterthan10% of biopsy sample must demonstrate infiltration by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation
3. Infiltrate should express typical immunophenotype: surface IgM+,CD19+, CD20+, CD22+, CD25+, CD27+, FMC7+, CD5 variable, CD10-, CD23-, CD103-, and CD108-.

The presentation of WM is a constellation of hyper-viscosity [1-4] autoimmune Hemolysis, and neuropathy.

This patient primarily presented with sensory neuropathy and necrotising soft tissue infection, the patient had had no prior history of hyper-viscosity or symptomatic anemia, there have been case reports of gangrenous necrosis associated with WM [4,5] expansive limb gangrene, bulbous cellulitis and gangrenous cholecystitis have also been reported. [16] In our case, recurrent hemolysis led to the suspicion of cold agglutinins, positive DAT (direct agglutination test), specific DAT for anti- C3d [4+] reactive at 4degrees with titre >1:1024 was diagnostic.

The occurrence of Cold agglutinin mediated hemolysisis a recognised entity in WM, however <5% will have Cold agglutinin disease (CAD) [7]. In WM, the monoclonal IgM para-proteins can present with cold auto immune hemolyticanaemia (AIHA).This Cold agglutination syndrome can occur secondary to CAD associated B cell neoplasms, marginal zonelymphoma, small lymphocytic lymphomaor LPL seen in WM isto be differentiated from Cold agglutination disease. Presence of marrow lymphoplasmacytic cells and the L265P mutation in the MYD88 gene is highly characteristic of WM. In a series of 232patientsreviewedin202 pathologists identified up to14% reported cases of CAD were due to WM. [23].

The IgM para proteins are directed against RBC antigens most commonly the I antigen. These then cause complement mediated extravascular haemolysis, however, during periods of stress intravascular hemolysis may be precipitated. The forces enabling antigen binding are characteristically weak, made stronger in cold temperatures due to reduced Brownian movement accounting for the cold reactivity.

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Cryoglobulins in contrast are cold precipitated immunoglobulins which do not bind to RBC surface. In WM both spectrums of disease are encountered where the large polyvalent IgM pentamerises and causes vascular occlusion leading to phenomenon of acrocyanosis as seen in our patient.

Due to the aberrant immunoglobulins along with associated hypogammaglobulinemia and reduced IgA and IgG infections, are commonly seen in WM, notably bacterial and respiratory tract infections. [17-18]In the past invasive fungal infections have also been reported. In this spectrum of paraproteinemias MGUS and MM increased risk of bacterial and viral infections [15]; there are reported cases of increased incidence of necrotisings of tissue infections [17,19] Most common findings in cases of NSTI as per reports are those of swelling (75%),erythema and pain beyond site of erythema; all of which were reported in our case on presentation.[20]

Early suspicion and prompt antibiotic initiation is crucial to reducesubsequent mortality and morbidity. We established Myonecrosis due the presence of heterogenous muscle density on USG limb which was then followed by MRI of the affected parts, an elevated CPK enzyme and resolution of infection as per empirical antibiotic initiation on meropenem, vancomycin and clindamycin. The LRINEC score is commonly used to differentiate NSTI from other soft-tissue infection scan help clinical decision between a conservative management (likeourcase) vs a surgical one. However, this core poses a challenge in neutropenic patients as in those that might been countered in MM/WM. While radiological evidence can suggest NSTI a strong clinical suspicion is required for early diagnosis in the disease course [20-22]. Notably, NSTI has also been reported with the treatment of Lenalidomidein MM in the past [19].

Nerve conduction studies conducted showed distal symmetric axonal- demyelination neuropathy in all limbs. Neurological complications are frequently found (20%) [11] in WM and occur as a result of hyper-viscosity, immunoglobulin deposition, direct infiltration by neoplastic lymphoplasmacytoid cells,or transformed high-gradelymphoma cells. They most commonly manifest as a distal, symmetric, slowly progressive sensorimotor peripheral neuropathy causing parasthesias and weakness [12]. The neuropathy in WM is usually demyelinating but certain studieshavereportedanaxonalpredominantpattern [13]. ParaproteinsIgM can act as autoantibody directed against myelin associated glycoproteins or other nerve components resulting in neuropathy [5,6] this resultsinadistalsymmetricprogressive demyelination sensory predominant neuropathy; motor axonal neuropathy Is more Common in disease like POEMS and amyloidosis. Other Neurological manifestations include cranial nerve palsies, mononeuropathy, mononeuritis multiplex, multifold leukoencephalopathy or infiltration of CNS (Bing-Neel syndrome) [14]. These symptoms show improvement with therapy but it has been reported that some degree of residual neuropathy still persists.

Treatment

Asymptomatic cases of WM donot warrant treatment. Treatment is initiated in the presence of certain clinical indications like hyper-viscosity, symptomatic lymphadenopathy (size >5cm), organomegaly, recurrent fever, night sweats, weight loss, peripheral neuropathy or lab indications likesymptomatic cryoglobulinemia, nephropathy, presence of hemolytic anemia, thrombocytopenia nephropathy. [8]

For newly diagnosed symptomatic WM, the first line of therapy is a combination of Rituximab (375mg/m2 on D1 of each cycle) and Bendamustine (90mg/m2 on D1 and 2 of each cycle) while continuous therapy with a BTK inhibitor like Ibrutinib, Zanubrutinib (more effective with a good safety profile) is proffered for older frail patients or non-consenting individuals. [9-10].

Conclusion

WM should be considered in elderly with unexplained weakness, neurological deficit, coagulopathy, visual difficulty and autoimmune haemolytic anemia. Although slow growing, with expansion of clonal LPL cells there is subsequent cytopenia manifesting as anemia, lymphadenopathyandhepatosplenomegaly.

In our case report our patient had manifestations of symmetric peripheral neuropathy which predated all other manifestations, evaluation for the same might have prevented the potentially life-threatening necrotising infection he subsequently presented with. This case report highlights the importance of considering atypical differentials when confronted with an absence of obvious alternatives.

Consent: The patient has signed a written informed consent form, agreeing to the publication of this case report and related medical images and lab reports.

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