



# Cold Agglutinin Disease in Non-Secretory Multiple Myeloma: A Case Report



Mahsa Abbaszadeh<sup>1\*</sup> , Hanieh Radkha<sup>2</sup> , Sahar Karimpour Reyhan<sup>1</sup> , Nasim Khajavi Rad<sup>1</sup>

1. Assistant Professor, Department of Internal Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.
2. Resident, Department of Internal Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online



**Citation** Abbaszadeh M, Radkha H, Karimpour Reyhan S, Khajavi Rad N. Cold Agglutinin Disease in Non-Secretory Multiple Myeloma: A Case Report. *Case Reports in Clinical Practice*. 2019; 4(4):110-114.

**Running Title** Cold Agglutinin Disease in Non-Secretory Multiple Myeloma



## Article info:

**Received:** 29 September 2019

**Revised:** 10 November 2019

**Accepted:** 21 November 2019

## Keywords:

Cold agglutinin; Multiple myeloma; Raynaud's phenomenon; Anemia

## ABSTRACT

Skin involvement is not common as the first manifestation of Multiple Myeloma (MM). Although extremely rare, leucocytoclastic vasculitis, plasmacytoma, autoimmune bullous disease, livedo reticularis and Raynaud's phenomenon may be the initial presentation of MM. Raynaud's phenomenon and livedo reticularis related to cold exposure can be due to Cold Agglutinin Disease (CAD) or cryoglobulinemia and can be seen as the first manifestation of MM. In this case study, we described a 55-year-old man complaining of limbs livedo reticularis and Raynaud's phenomenon during cold weather. Further evaluations revealed anemia and elevated ESR. Skull X-ray showed multiple punched-out lesions. Finally, serum protein electrophoresis and bone marrow aspiration confirmed the diagnosis of non-secretory MM as the underlying disease of CAD. The patient was referred to the hematologist for the treatment of MM.

## Introduction

C

old Agglutinin Disease (CAD) is a hemolytic anemia characterized by the presence of cold-related clinical symptoms. The main pathology is due to the antibodies directed against polysaccharide antigens on

the red blood cell surface. This condition may occur as a benign CAD or secondary to infections, malignancy, or autoimmune disease.

Multiple Myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing abnormal immunoglobulin proteins. Plasma cells proliferate in bone marrow and often result in extensive skeletal de-

\* Corresponding Author:

**Mahsa Abbaszadeh, PhD.**

**Address:** Department of Internal Medicine, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

**E-mail:** [m-abbaszadeh@sina.tums.ac.ir](mailto:m-abbaszadeh@sina.tums.ac.ir)



**Figure 1.** Livedo reticularis and Raynaud's phenomenon following exposure to the cold weather



struction with osteolytic lesions, osteopenia, and pathologic fractures [1].

We present a 55-year-old man with complaints of limbs livedo reticularis and Raynaud's phenomenon during cold weather. Our findings suggested CAD as an initial symptom of MM. Only few cases of CAD associated with MM have been reported [2, 3]. This case illustrated the relation of CAD and hypogammaglobulinemia with MM.

### Case Presentation

A 55 years old previously healthy man presented with limbs livedo reticularis and Raynaud's phenomenon during cold weather, malaise, and weakness.

Further questioning revealed vertigo, headache, dyspnea and paresthesia dominantly presented during cold weather. Physical examination revealed an oriented and cooperative man. His vital signs were as follows: body temperature 37.8°C (oral), blood pressure 110/70 mm Hg, pulse rate 105 beats per minute, and respiratory rate 18 breaths per minute. He was pale and had cold-related discoloration of upper limbs. His head and neck examination results were unremarkable. Cardiopulmonary, abdominal, and neurological examinations were also unremarkable. Hepatomegaly or splenomegaly was not detected. No lymph nodes were palpable in his neck, axilla, groin, and popliteal regions (Figure 1).

The following laboratory results were obtained as follows: Hemoglobin= 2.6 g/dL, White Blood Cells (WBC)= 5300/mL, platelet= 36000/mL, Mean Corpuscular Volume (MCV)= 98 fL, Erythrocyte Sedimentation Rate (ESR)= 125 mm/h, Lactate Dehydrogenase (LDH)= 734

U/L, corrected reticulocyte count= 4, Ca= 8.5 mg/dL and Cr= 1.1 mg/dL. The patient's blood samples were agglutinated rapidly in room temperature (Figure 2).

Peripheral Blood Smear (PBS) revealed rouleaux formation. Serum viscosity was 1.7 (normal [NL] range: 1.4-1.8). Qualitative blood cold agglutinin test was 3+ and urine test for Bence Jones protein was negative. Serum protein electrophoresis was abnormal in gamma globulin concentration, which was 6.5% (NL: 12-20%). No monoclonal peak was observed. However, hypogammaglobulinemia was found. The following results were also obtained: albumin: 53.4% (NL: 53-63%), alpha1: 3.8% (NL: 1.5-4.5%), alpha2: 19.8% (NL: 6-12%), gamma: 6.5% (NL: 12-20%), beta: 15.7% (NL: 11-17%), plasma IgA: 0.9 g/L (NL: 0.71-3.5 g/L), IgM: 0.6 g/L (NL: 0.4-2.63 g/L), IgE: 20.2 g/L (NL<100 g/L), and IgG: 2.9 g/



**Figure 2.** The patient's blood samples were agglutinated rapidly in room temperature





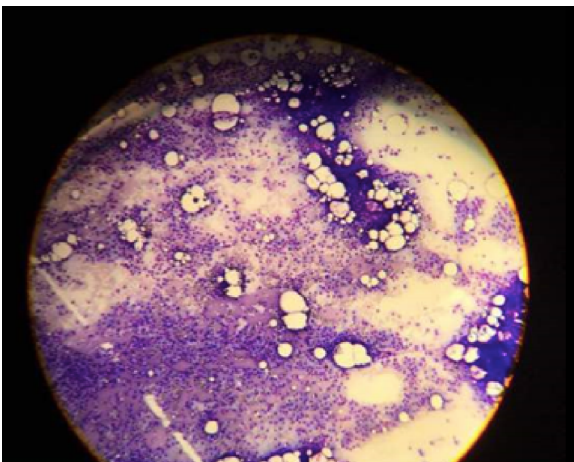
**Figure 3.** Multiple punched out lytic lesions on skull x-ray

dL (NL: 6.5-13.5 g/dL). Electrophoresis of urine specimen demonstrated no detected protein. In conclusion, protein electrophoresis was compatible with non-secretory MM.

The skull x-ray revealed multiple punched out lytic lesions (Figure 3).

Bone marrow aspiration and biopsy showed more than 60% of the clonal plasma cells in the specimen, typical for MM (Figure 4).

After transfusion of the packed red blood cell and avoidance of cold exposure, symptoms of hemolytic anemia were relatively resolved. The patient was referred to the hematologist for the treatment of MM.



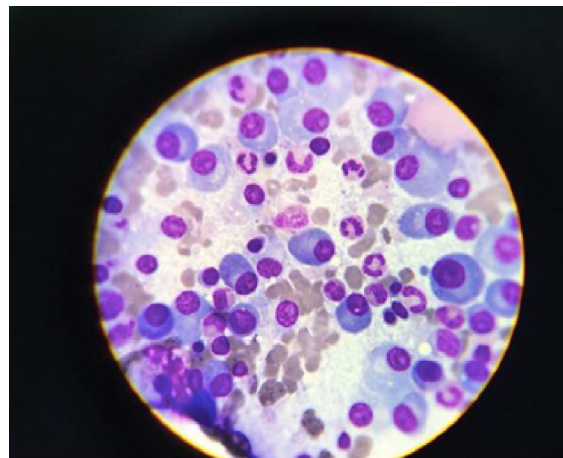
## Discussion

CAD is a haemolytic anemia characterized by the presence of cold-related clinical symptoms. The symptoms are associated with anemia (fatigue, weakness, dyspnea on exertion) and red blood cell agglutination at low temperatures (acrocyanosis, Raynaud's phenomenon, and livedo reticularis). The main pathology is due to the antibodies directed against polysaccharide antigens on red blood cell surface.

This condition may occur as a benign primary CAD or secondary to infections (viral infections, such as Epstein-Barr virus, cytomegalovirus, HIV, influenza, etc. or bacterial infections, such as mycoplasma, *Escherichia coli*), lymphoid and non-lymphoid malignancies or an autoimmune disease. More than 70% of cases have one of these associated conditions. [4]

Cryoglobulinemia is another cold-related pathologic condition, in which precipitation of blood proteins at the temperatures lower than 37°C can be observed. Cryoglobulinemia (CG) type I (5-25% of CG), including an isolated monoclonal Ig (typically IgG or IgM) can present the signs of hyperviscosity resulted from high levels of monoclonal CG. This condition classically presents possible signs related to hyperviscosity, thrombosis, Raynaud phenomenon, digital ischemia, livedo reticularis, and purpura [5, 6]. In severe cases, without treatment, this may progress to gangrene. It is usually associated with a hematologic malignancy, such as Waldenström's Macroglobulinemia (WMG) or MM [7, 8, 9].

Based on Raynaud's phenomenon, livedo reticularis during cold weather, and rapid agglutination of blood



**Figure 4.** Bone marrow aspirate smear revealing an increase in plasma cells



samples at room temperature, our differential diagnosis was limited to the following disorders: WMG, CAD, CG, and vasculitis. The presence of an IgM monoclonal gammopathy in the serum is one of the most important criteria in diagnosis of WM. The quantitative IgM level, which obtained in the warm serum sample of the patient was 0.6 g/L (NL: 0.4-2.63 g/L).

Serum protein electrophoresis and immunology did not show any increase in IgM level. In addition, serum viscosity was 1.7 mPas with the normal range of 1.4-1.8 mPas. Therefore, analysis of the serum protein components did not support the diagnosis of WM. Furthermore, according to the concurrent haemolytic anemia, normal serum viscosity and positive qualitative cold agglutinin test, the most probable diagnosis was CAD. Unfortunately, we could not check the cryoglobulin. Additional findings, such as more than 60% of clonal plasma cells in the bone marrow specimen as well as punched out lesions in skull x-ray supported the diagnosis of MM as the underlying disease.

Although severe anemia was not expected in CAD, bone marrow plasma cell infiltration interfering with compensatory erythroid hyperplasia and prolonged hemolysis caused an unusual severe anemia in the patient. Anemia in CAD is usually considered to be mild to moderate and the hemoglobin level of lower than 6 g/dL has been reported rarely [4, 10].

The definite diagnosis of CAD in a patient complaining of discomfort in exposure to cold is confirmed by observing all the following criteria: red blood cell aggregation on peripheral blood smear, presence of a high titer of cold agglutinins, positive direct antiglobulin (Coombs) test (the test is usually negative for bounded IgG).

CAD may occur as a primary Cold Agglutinin Disease or secondary to the infections and malignancies. Swiecicki et al. conducted a retrospective study on 89 patients with CAD from 1970 to 2012. They detected an underlying hematologic disorder in 78% of the patients. In their survey, 76% of the patients were alive 5 years after the diagnosis [4]. Berentse evaluated bone marrow histology in 66 patients with primary CAD. Lymphoproliferative B-cell disorder was detected in histologic findings of 76% of the samples [11].

Protein electrophoresis of our patient was compatible with non-secretory MM and showed hypogammaglobulinemia. Serum protein electrophoresis can demonstrate a localized band or peak in 82% of the patients with myeloma [12]. Addition of serum protein

immunofixation increases the sensitivity to 93%. It can be increased to 97% or more by performing the serum free light chain assay or urine protein electrophoresis and immunofixation [12]. Patients with no detectable M protein using these tests are considered to have "non-secretory myeloma". Of 20% of cases with no localized band on SPES, hypogammaglobulinemia is seen in approximately one half (partially due to suppression of normal gamma globulin production) with no apparent abnormality in the remainder [12].

Furthermore, there is another challenge about variants of MM, which are called "false non-secretors." These are MM variants or related plasma cell diseases with measurable intracellular immunoglobulin by immunofluorescence, whereas they are not measurable extracellular components via typical testing. It has been suggested that these immunoglobulins are secreted in vesicles via budding of the cell membrane, rendering them undetectable in the serum [13].

Treatment of CAD includes avoidance of cold, glucocorticoids, plasmapheresis, alkylating agents, rituximab-containing regimens, and other cytotoxic agents. In the presence of underlying lymphoproliferative disorder, appropriate chemotherapy is recommended. Chemotherapy of the underlying disease can treat the concomitant CAD.

## Ethical Considerations

### Compliance with ethical guidelines

All of the authors conduct themselves in accordance with professional ethics.

### Funding

This work is supported in part by the Imam Khomeini Hospital Complex Research Center.

### Conflict of interest

The authors declared no conflict of interest.

## References

- [1] Kariyawasan CC, Hughes DA, Jayatilake MM, Mehta AB. Multiple myeloma: Causes and consequences of delay in diagnosis. *QJM: An International Journal of Medicine*. 2007; 100(10):635-40. [DOI:10.1093/qjmed/hcm077] [PMID]



- [2] Khatun H, Afrose S, Khan MH, ARA T, Islam S. Cold agglutinin disease secondary to multiple myeloma in a psoriatic patient. *Journal of Medicine*. 2014; 15(2):141-3.
- [3] Ravindran A, Kyle R, Sankaran J, Jacob E, Kreuter J, Christopher Hook C, et al. High prevalence of monoclonal gammopathy among patients with warm autoimmune hemolytic anemia. *American Journal of Clinical Pathology*. 2016; 146(Suppl-1):180. [DOI:10.1093/ajcp/aqw151.041]
- [4] Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood*. 2013; 122(7):1114-21. [DOI:10.1182/blood-2013-02-474437] [PMID]
- [5] Monti G, Galli M, Invernizzi F, Pioltelli P, Saccardo F, Monteverde A, et al. Cryoglobulinaemias: A multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease; GISC. Italian Group for the Study of Cryoglobulinaemias. *QJM: An International Journal of Medicine*. 1995; 88(2):115-26. [PMID]
- [6] Payet J, Livartowski J, Kavian N, Chandresis O, Dupin N, Wallet N, et al. Type I cryoglobulinemia in multiple myeloma, a rare entity: Analysis of clinical and biological characteristics of seven cases and review of the literature. *Leukemia & Lymphoma*. 2013; 54(4):767-77. [DOI:10.3109/10428194.2012.671481] [PMID]
- [7] Ng YC, Schifferli JA. Clearance of cryoglobulins in man. *Springer Seminars in Immunopathology*. 1988; 10(1):75-89. [DOI:10.1007/BF02054025]
- [8] Terrier B, Karras A, Kahn JE, Le Guenno G, Marie I, Benarous L, et al. The spectrum of type I cryoglobulinemia vasculitis: New insights based on 64 cases. *Medicine*. 2013; 92(2):61-8. [DOI:10.1097/MD.0b013e318288925c] [PMID] [PMCID]
- [9] Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. *The Lancet*. 2012; 379(9813):348-60. [DOI:10.1016/S0140-6736(11)60242-0]
- [10] Barcellini W, Fattizo B, Zaninoni A, Radice T, Nichele I, Di Bona E, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: A GIMEMA study of 308 patients. *Blood*. 2014; 124(19):2930-6. [DOI:10.1182/blood-2014-06-583021] [PMID]
- [11] Berentsen S. How I manage cold agglutinin disease. *British Journal of Haematology*. 2011; 153(3):309-17. [DOI:10.1111/j.1365-2141.2011.08643.x] [PMID]
- [12] Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings*. 2003; 78(1):21-33. [DOI:10.4065/78.1.21] [PMID]
- [13] Dupuis MM, Tuchman SA. Non-secretory multiple myeloma: From biology to clinical management. *OncoTargets and Therapy*. 2016; 9:7583-90. [DOI:10.2147/OTT.S122241] [PMID] [PMCID]