DOI: 10.4274/gulhane.galenos.2026.58257
Gulhane Med J 2026;68(3):208-211

CD20-positive multiple myeloma complicated by cold agglutinin disease

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Cite this article as: Keskin D, Özer HC, Candan Ö, Altay AY, Akarsu M. CD20-positive multiple myeloma complicated by cold agglutinin disease. *Gulhane Med J.* 2026;68(3):208-211

Date submitted:
08.10.2025
Date accepted:
28.01.2026
Publication Date:
18.09.2026

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Keywords:
Multiple myeloma, cold agglutinin, CD20, hemolytic anemia

ABSTRACT

Cluster of differentiation 20 (CD20) expression is rarely observed in multiple myeloma (MM) and is typically associated with immature plasma cell morphology and aggressive clinical behavior. Cold agglutinin disease (CAD) is also uncommon in MM and usually suggests other hematologic malignancies. We present a rare case of CD20-positive MM complicated by CAD in a 77-year-old woman who initially had pancytopenia, bone pain, and renal failure. Diagnostic work-up revealed light chain MM with kappa restriction, cast nephropathy, and diffuse CD20 expression in plasma cells. She was treated with bortezomib, cyclophosphamide, and dexamethasone (VCD), achieving hematologic improvement and partial renal recovery. During the third cycle, she developed severe anemia and hemolysis due to cold agglutinins, which were managed successfully with corticosteroids and supportive care. Retrospective immunohistochemistry confirmed CD20 positivity. This case underscores the diagnostic and therapeutic complexity of atypical MM presentations and highlights the importance of re-evaluating immunophenotypic features when the clinical course deviates from expectations. While CD20-targeted therapies are not routinely used in MM, their relevance in selected subtypes warrants further exploration. Our case illustrates the potential for paraneoplastic hemolysis and phenotypic diversity in MM, emphasizing the need for a multidisciplinary approach to diagnosis and management.

Introduction

Cluster of differentiation 20 (CD20) is typically absent in terminally differentiated plasma cells and is not routinely expressed in plasma cell dyscrasias. Its expression is often associated with immature or plasmablastic morphology and has been linked to more aggressive clinical behavior (1). Cold agglutinin antibodies are also rarely reported in the context of multiple myeloma (MM), and their presence typically prompts investigation for alternative underlying hematologic malignancies such as lymphoma (2). Herein, we describe an unusual case of MM with both CD20 positivity and cold agglutinin hemolytic anemia, highlighting the diagnostic complexity and potential therapeutic implications.

Case Report

A 77-year-old woman was admitted with pancytopenia and subacute renal failure. She had a recent history of analgesic use, and the initial evaluation suggested acute tubulointerstitial nephritis, which prompted treatment with methylprednisolone (0.5 mg/kg/day). Laboratory workup revealed the following values: hemoglobin 6.9 g/dL; neutrophils 660/mm^3; platelets 81.000/mm^3; serum creatinine 2.99 mg/dL; and urea 105 mg/dL. Hematology consultation was requested after progressive cytopenias were noted. Peripheral smear revealed teardrop cells and a leukoerythroblastic picture; there was no organomegaly, but the patient reported widespread bone pain. The reticulocyte count was low, consistent with hypoproliferative anemia. Steroids were discontinued. Bone marrow aspiration was attempted but resulted in a dry tap. Imprint smears showed an increased number of plasma cells, but the findings were initially non-diagnostic. Due to a dry tap during bone marrow aspiration, fluorescence *in situ* hybridization analysis could not be performed; therefore, the status of t(4;14) and t(11;14) translocations remains unknown.

Renal biopsy demonstrated tubular cast formation and associated inflammation. The presence of kappa light chain-positive casts was consistent with cast nephropathy, with no evidence of neoplastic plasma cells (Figure 1). Serum protein electrophoresis showed immunoparesis without an M spike. Serum free light- chain levels were low. Bone marrow biopsy showed infiltration by CD138+, CD38+, MUM1+, kappa+ atypical plasma cells (Figure 2). Expression of Cyclin D1 and c-*MYC* was observed, and reticulin fibrosis ranged from moderate to severe. Congo red staining was negative.

Serum and urine immunofixation revealed kappa monoclonality. The free kappa and lambda light chains were 136 mg/L and 3.84 mg/L, respectively. Positron emission tomography-computed tomography showed diffuse axial marrow fluorodeoxyglucose (FDG) uptake and mild splenic FDG uptake (maximum standardized uptake value 4.6), suggesting extramedullary involvement. Based on these findings, a diagnosis of light-chain MM was made, and treatment with a bortezomib, cyclophosphamide, and dexamethasone (VCD) regimen was initiated. The patient showed improvement in cytopenias with complete resolution of neutropenia and thrombocytopenia. Renal function partially recovered, and a partial hematologic response was achieved.

During the third cycle of therapy, the patient presented with severe anemia (hemoglobin: 4.9 g/dL), jaundice, and fatigue. Despite negative direct and indirect Coombs tests, cold agglutinin antibodies were detected qualitatively, and the titer was not assessed. Serum lactate dehydrogenase level was 335 U/L, serum C3 was 1 g/L, and serum C4 was 0.35 g/L. High-dose methylprednisolone (1 mg/kg/day) was administered. Citrate-treated, crossmatched blood transfusions were administered without reaction, and the hemoglobin concentration improved to 11.6 g/dL. The patient died of coronavirus disease-19 (COVID-19) infection shortly after cold agglutinin disease (CAD) resolved.

Retrospective immunohistochemical analysis of the initial bone marrow biopsy performed after the onset of CAD revealed diffuse CD20 expression in plasma cells (Figure 2). While this did not alter the initial therapeutic strategy, the co-occurrence of CD20 expression and CAD raises important considerations regarding the potential for alternative or adjunctive therapeutic approaches in similar future cases.

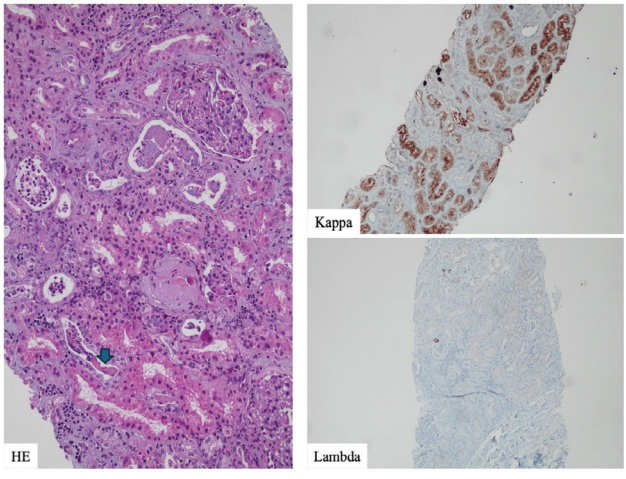

Figure 1. The pathological findings of the renal biopsy specimen. Renal biopsy specimen showing no infiltration of neoplastic plasma cells. The arrow indicates eosinophilic amorphous material within the tubular lumen in a focal area, consistent with kappa-positive cast nephropathy (H&E stain, magnification ×30)

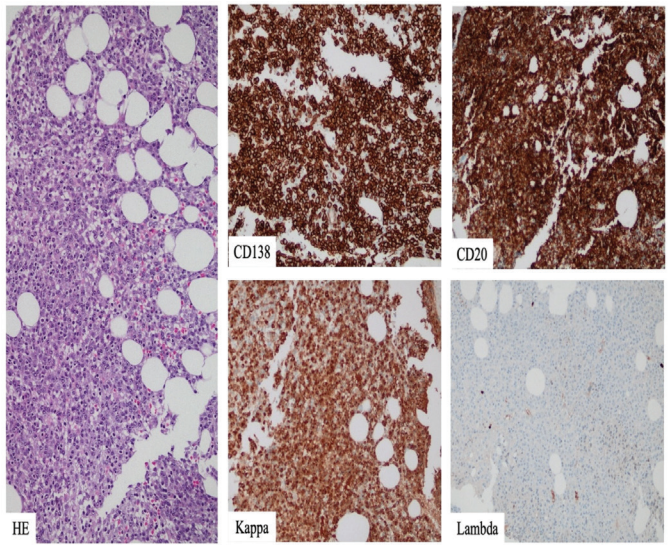

Figure 2. The bone marrow biopsy findings. Bone marrow biopsy showing sheets of neoplastic plasma cells on H&E staining (magnification ×30). Immunohistochemical analysis demonstrated diffuse CD20 positivity in nearly all plasma cells

CD: Cluster of differentiation

Discussion

CD20 is a transmembrane phosphoprotein functioning as a calcium ion channel on the B-cell membrane, involved in activation and differentiation. Its biological significance in plasma cells remains uncertain (3). CD20 expression is rare in MM, representing deviation from the conventional plasma cell immunophenotype and suggesting clonal heterogeneity or an alternative differentiation pathway (4). In a study by Yavasoglu et al. (3) including 61 MM cases, CD20 positivity (>10%) was observed in 48.9% of patients. Similarly, Li et al. (5) analyzed 62 CD20-positive MM cases and found that this phenotype was often associated with t(11;14) translocation, lower CD56 expression, and reduced extramedullary disease, suggesting a distinct biological subset.

Khatun et al. (6) reported a psoriatic patient with cold agglutinin disease secondary to non-immunoglobulin M (IgM) MM, manifesting hepatomegaly rather than splenomegaly, and a lymphoma-like disease course. CD20 expression was not evaluated in that case.

Cold agglutinins are IgM antibodies that bind erythrocytes at low temperatures, leading to complement-mediated hemolysis. They are most often seen in lymphoproliferative disorders or secondary to infections and autoimmune diseases (7). No secondary cause was identified in our patient, suggesting a paraneoplastic mechanism directly related to MM (8). The coexistence of cold agglutinin hemolytic anemia and mildly FDG-avid spleen prompted re-evaluation for B-cell markers, revealing CD20 expression on plasma cells-an unexpected feature in typical MM. This observation underscores that, in MM patients presenting with immune cytopenias and subtle splenic findings, CD20-positive plasma cell disease should be considered in the differential diagnosis.

Similarly, cold-induced cutaneous manifestations initially attributed to cold agglutinin disease have been linked to underlying MM, highlighting the need to investigate hematologic malignancies in such presentations. While the previously reported case lacked organomegaly or lymphadenopathy (9), our patient exhibited non-palpable splenomegaly and increased FDG uptake in the spleen, compatible with a lymphoplasmacytic pattern or CD20-positive MM. Differential diagnosis such as Waldenström macroglobulinemia were considered; however, the absence of lymphoplasmacytic infiltration and IgM monoclonal protein supported the diagnosis of CD20-positive multiple myeloma. Kidney pathological findings and the patient's clinical presentation were compatible with multiple myeloma instead of Waldenström macroglobulinemia.

Our patient demonstrated kappa light chain restriction, CD20 expression, suspected splenic involvement, and cold agglutinin-mediated hemolysis, reflecting the biological diversity of MM. Although anti-CD20 therapy is not standard in MM, its potential role in CD20-positive subtypes warrants further study (10-12). Notably, recent data suggest that CD20 expression in MM may define a subgroup with small mature plasma cell morphology and t(11;14) translocation, which may exhibit indolent clinical behavior but distinct treatment response profiles (1,13). Our patient responded favorably to corticosteroids and VCD without rituximab, but the retrospective identification of CD20 expression highlights its possible prognostic and therapeutic implications in atypical or refractory cases. Although CD20 expression in MM is rare, anti-CD20 monoclonal antibody therapy (rituximab) has been used in isolated cases. However, evidence regarding clinical benefit or prognostic impact remains limited. Unfortunately, our patient developed a COVID-19 infection shortly after starting steroid treatment; the anemia improved during that treatment. Therefore, rituximab was not used.

According to the study by Khaled et al. (14), CD20 expression may emerge at relapse as a secondary genetic event linked to disease aggressiveness, proposing its role as a prognostic and therapeutic marker. Early CD20 expression, as observed in our patient, may therefore represent an immunophenotypic shift along the B-cell to plasma-cell continuum.

Mohamed et al. (15) described a 69-year-old woman with primary CAD and a small clonal plasma cell population who achieved transfusion independence with daratumumab after rituximab failure. This highlights daratumumab as a potential option for refractory CAD associated with clonal B-cell disorders and suggests that it may have implications for CD20-positive MM with immune cytopenias.

IgA-type plasma cell neoplasia presenting with cold agglutinin-mediated hemolytic anemia, as exemplified by our patient, has also been documented in the literature, underscoring the necessity of comprehensive clinicopathological correlation to ensure accurate diagnosis of such atypical presentations (16).

This case illustrates a rare MM phenotype characterized by CD20 expression, CAD, and kappa light chain-associated cast nephropathy. It emphasizes the importance of re-evaluating the immunophenotype in MM patients with immune-mediated cytopenias or organ involvement, and supports multidisciplinary correlation for accurate classification and optimized management.

Ethics

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.C.Ö., A.Y., M.A., Concept: D.K., Ö.C., Design: D.K., H.C.Ö., Ö.C., A.Y., Data Collection or

Processing: D.K., H.C.Ö., A.Y., M.A., Analysis or Interpretation: D.K., Ö.C., A.Y., Literature Search: D.K., Ö.C., Writing: D.K., Ö.C.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: The authors declare that this study received no financial support.

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