

Waldenstrom's Macroglobulinemia terminating in acute Myeloid Leukemia

Safoorah Khalid, Salman Naseem Adil, Mohammad Khurshid
Department of Pathology and Microbiology, Aga Khan University Hospital, Karachi.

Abstract

Waldenstrom's macroglobulinemia (WM) is a rare condition, accounting for approximately 2% of haematologic malignancies. The most common causes of death in these patients are progression of the malignant lymphoproliferative process, infection and cardiac failure. Acute leukemia is a rare event in the clinical course of WM. A number of case reports have documented the development of terminal acute leukemia in patients with WM following prolonged chemotherapy.

We describe a case of an elderly man who was a diagnosed case of WM and treated with chlorambucil and cyclophosphamide. Four years later, he developed acute leukemia.

Introduction

Waldenstrom's macroglobulinemia (WM) is a rare condition, accounting for approximately 2% of haematologic malignancies.¹ It is almost entirely a disease of elderly, with a peak incidence in the sixth and seventh decades. Clinically overt WM may follow a long period of benign monoclonal gammopathy. The common presenting features are weakness and fatigue, haemorrhagic manifestations, weight loss, neurologic symptoms, visual disturbances and Raynaud's phenomenon. As the disease progresses, hepatomegaly, splenomegaly and lymphadenopathy become prominent features. In WM, the signs and symptoms of hyperviscosity syndrome are related to the circulatory disturbances caused by the increased resistance to blood flow. Conventional treatment regimen includes alkylating agents such as chlorambucil or cyclophosphamide. The most common causes of death in these patients are progression of the malignant lymphoproliferative process, infection and cardiac failure.² The development of acute leukemia has also been rarely described as a preterminal event and it has been reported to occur following prolonged chemotherapy with alkylating agents in majority of the cases.

Case Report

A 75 years old gentleman presented in September 2001 with history of angina. General physical examination revealed pallor. There was no evidence of lymphadenopathy and hepatosplenomegaly. Laboratory data were as follows: haemoglobin 9.1gm/dl, WBC $9.6 \times 10^9/L$, platelets $230 \times 10^9/L$ and ESR 108 mm/hr.

A bone marrow was done which revealed 40% lymphoplasmacytoid and plasma cells. Immunofixation

electrophoresis showed IgM kappa light chains. Serum IgM levels were found to be 42.2gm/dl. Thus he was diagnosed to have WM. Chlorambucil was prescribed at the dose of 10mg/day for twelve months followed by cyclophosphamide 150mg/day for fifteen days every month for four months. He also required off and on packed cell transfusions during the course of his treatment.

In March 2005, he presented with pallor and altered behaviour and speech. Examination was unremarkable. His CBC revealed haemoglobin 9.7gm/dl, WBC $29.8 \times 10^9/L$, platelets $30 \times 10^9/L$, 40% blast cells were present on the peripheral film and bone marrow findings were consistent with acute myeloid leukemia. The patient refused further treatment and died within one month.

Discussion

The development of terminal acute leukemia in patients with WM appears to be a rare event. Literature review reveals various case reports.³⁻⁶ A vast majority of WM were complicated by acute myeloid leukemia. However, one case of acute lymphoid leukemia has been reported.⁶ A therapy-related myelodysplastic syndrome during the course of WM has also been observed in rare patients.⁷ In most of them, the condition developed after treatment with alkylating agents. It may also occur rarely in an untreated case of WM.⁸

In majority of cases including ours, there was a history of treatment with one of the alkylating agents. In contrast, acute leukemia rarely complicates chronic lymphocytic leukemia even with long term treatment with alkylating agents. The rarity with which acute leukemia is encountered in this disorder would suggest that in the well differentiated lymphoproliferative disorders, alkylating agents are not involved in leukemogenesis.⁹ Although in those patients who received treatment for their WM, acute leukemia secondary to this therapy seems to be the most widely accepted etiological theory; the possible etiology of non-treated cases remains controversial.¹⁰ One theory postulates that leukemia may have arisen from a different clone of cells either secondary to the same etiologic agent that produced the WM or secondary to another etiologic factor.⁵

Response to treatment is poor and survival is very short.⁵ In light of various case reports including ours, leukemogenic potential of alkylating agents in WM would

appear to warrant further scrutiny.

References

1. Dimopoulos MA, Alexanian R. Waldenstrom's macroglobulinemia. *Blood* 1994; 83:1452-9.
 2. Kyle RA, Garaton JP. The spectrum of IgM monoclonal gammopathy in 430 cases. *Mayo Clin Proc* 1987;62:719-31.
 3. Frobbs IJ. Development of acute leukemia after prolonged treatment with chlorambucil. *Med J Aust* 1972;11:918-9.
 4. Rosner F, Grunwald HW. Multiple myeloma and Waldenstrom's macroglobulinemia terminating in acute leukemia. *N Y State J Med* 1980;80:558-70.
 5. Rodriguez JN, Jurado AF, Martino ML, Prados D. Waldenstrom's macroglobulinemia complicated with acute myeloid leukemia: Report of a case and review of the literature. *Haematologica* 1998;83:91-4.
 6. Madan RA, Chang VT, Baddoura FK, Srinivas S, Kasimis B. Waldenstrom's macroglobulinemia evolving into acute lymphoblastic leukemia: a case report and review of the literature. *Leukemia* 2004;18:1433-5.
 7. Shin SJ, Chun SH, Kim KO, Kim MK, Lee KH, Hyun MS, Cho HS. Myelodysplastic syndrome with complex karyotypic abnormalities in a patient with Waldenstrom's macroglobulinemia after sequential treatment with chlorambucil and fludarabine. *Jpn J Clin Oncol* 2005;35:622-5.
 8. Murashige N, Tabanda R, Zalusky R. Occurrence of acute monocytic leukemia in a case of untreated Waldenstrom's macroglobulinemia. *Am J Hematol* 2002; 71:94-7.
 9. Mackenzie MR, Fundenberg HH. Macroglobulinemia: an analysis of 40 patients. *Blood* 1972;39:874-89.
 10. Horsman DE, Card RT, Skinnider LF. Waldenstrom's macroglobulinemia terminating in acute leukemia: a report of three cases. *Am J Hematol* 1983;15:97-101.
-