

## Case Report

# Rapid evolving into acute myeloid leukemia in a patient with multiple myeloma and concurrent myelodysplasia after VTD therapy

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**Abstract:** The association of Myelodysplasia (MDS) and multiple myeloma (MM) has been usually described not only as a complication of chemotherapy but also in the absence of preceding chemotherapy or together at the time of diagnosis. Optimal therapies of a coexisting MM and MDS have not been well established up to now. We report a case of MDS diagnosed simultaneously with MM. After treatment with VTD (bortezomib, thalidomide, dexamethasone) marked anti-myeloma activity was observed, but it was associated with rapid progression of the MDS to acute myeloid leukemia (AML). The leukemic transformation in our case most probably reflects the natural progression of MDS, though it clearly demonstrates that VTD is ineffective in controlling blast proliferation in MDS. To our knowledge, this is the first case report on MDS in the setting of MM with rapid evolution to AML to VTD therapy. More data from more cases are needed, to find the potential utility of VTD therapy in coexisting MDS and MM patients.

**Keywords:** VTD, multiple myeloma, myelodysplasia, acute myeloid leukemia

## Introduction

Myelodysplasia (MDS) has been described as a late complication of chemotherapy with alkylating agents in patients treated for multiple myeloma (MM). Despite its rarity, there are reports on coincidence of MDS and MM, unrelated to therapy as well. Non-treatment-related factors are less well understood but may play significant roles. Potential disease-related risk factors include baseline complex cytogenetics and the subtype of myeloma [1, 2]. We report here a case of MDS diagnosed simultaneously with myeloma, where clinical management of a coexisting MM and MDS represents a major challenge.

## Case report

A 75-year-old man presented with a one-month history of increasing fatigue and anorexia, but no adenopathy or bleeding. On examination the only positive physical finding was pallor. A complete blood count (CBC) showed hemoglobin 83 g/L, leukocyte count  $2.2 \times 10^9/L$  (with normal

differential) and platelet count  $43 \times 10^9/L$ . His erythrocyte sedimentation rate was 130 mm/h, and his total protein level was 9.5 g/L with 3.2 g/L albumin. His  $\beta_2$ -microglobulin level was 5.38 mg/L. Immunoelectrophoresis showed monoclonal increase in serum immunoglobulin with IgA and  $\lambda$  light chain. The levels of IgG and IgM were low. The rest of the routine chemistry profile was normal. A radiographic skeletal survey revealed lytic lesions in the skull. A peripheral blood film showed macrocytosis. A bone marrow aspirate was hypercellular. Erythropoiesis showed marked dyserythropoietic changes with karyorrhexis, cytoplasmic vacuolation and binucleate erythroid precursors. Myelopoiesis was generally normal, but occasional hypogranular myelocytes were present. Megakaryocytes were normal. Plasma cells accounted for 12% of the myelogram. Marrow iron stores were increased: no ring sideroblasts were seen. Banded chromosomal analysis of the marrow cells revealed a complex karyotype (**Table 1**). A diagnosis of MM IgA lambda with MDS type RCUD (refractory cytopenia with unilineage dysplasia) was made.

After written informed consent, the patient was given bortezomib at a dose of 1.3 mg/m<sup>2</sup> on days 1, 4, 8 and 11 of a 28-day cycle, along with 20 mg dexamethasone at the same schedule and 100 mg thalidomide everyday. After two cycles of VTD, the patient presented a 75% reduction in serum IgA/λ level and normal β<sub>2</sub>-microglobulin level. He achieved a partial remission. Therapy was complicated by prolonged pancytopenia and infection of varicella zoster virus (grade 2). The blood transfusions and granulocyte colony-stimulating factor were administered for supportive care. The treatment was discontinued and the patient was lost to follow-up. Two months later, he presented again with cough, fever, and purulent expectoration. X-rays of the lung showed bronchopneumonia. CBC showed hemoglobin 85 g/L, leukocyte count 38.6 × 10<sup>9</sup>/L with 65% blasts, platelet count 10 × 10<sup>9</sup>/L. The bone marrow was hypercellular with 85% blasts and no plasma cells, which confirmed this progression to AML. Interestingly, serum IgA value decreased near to normal level despite persistence of low IgG and IgM levels and increased β<sub>2</sub>-microglobulin serum concentration. The patient requested supportive therapy only and he died from a brain hemorrhage one week after admission to the hospital. No autopsy was performed.

### Discussion

MM is complicated in 4-10% of cases by MDS, generally terminating in AML [1]. The association of MDS after treatment of myeloma is well established. However, MDS very rarely occurs during the course of untreated MM. Some reports on the simultaneous occurrence of MDS and MM or the occurrence of this secondary disorder without preceding chemotherapy, have led to the hypothesis that MM and MDS could originate from a defect in a common progenitor stem cell [2].

Cytogenetic aberrations of MM have been well characterized, and its prognostic significance has been established [3-5]. MM-MDS denotes a MM karyotype that contains cytogenetic patterns characteristic of MDS [-5; 5q; -7; 7q; +8; t(1;7); 20q]. The patients bearing the MM-MDS signature karyotype belong to those of poorest outcome despite tandem transplants [3]. In our patient, a complex karyotypes, hypodiploidy,

and certain total or partial loss of chromosomes 5, 13 and 17 was identified at diagnosis. Simultaneous occurrence of MDS and MM in the patient suggests a neoplastic transformation of a pluripotent stem cell rather than a chance association.

The treatment of MM has evolved substantially over the last decade, agents with new mechanisms of action, such as bortezomib, thalidomide, and lenalidomide, have resulted in considerable improvements in outcome. Combining agents with different mechanisms of action may potentially improve efficacy. We have conducted VTD for patients with MM, and the overall response rate was 91% [6].

Bortezomib is a potent, reversible, and specific inhibitor of the proteasome approved for use in multiple myeloma. Bortezomib affects myeloma cell growth by NF-κB blockade, downregulation of adhesion molecules, inhibition of angiogenesis and by inhibiting DNA repair, all of which results in a proapoptotic effect on myeloma [7]. The inhibitory effect on NF-κB of bortezomib has made it an attractive agent for MDS therapy. However, comparatively few studies have evaluated the therapeutic efficacy and mechanism of bortezomib in MDS [8, 9]. One possible mechanism of the action of bortezomib in higher-risk MDS may be cytokine-mediated [8].

Thalidomide induces apoptosis of plasma cells directly, blocks adhesion of myeloma cells to marrow stromal cells, reduces the levels of angiogenesis factors and inhibits angiogenesis [10]. Thalidomide has reported activity in MDS with improved peripheral cytopenia and decreased transfusion requirements. The studies showed the patients with high-risk MDS treated with thalidomide, probably attributable to a modulation of blast interaction with the bone marrow microenvironment, rather than to a cytotoxic effect of the drug on the malignant cell [11].

MM is a disease where protection against or resistance to apoptosis may be important in expansion of the clone and/or resistance to therapy. Ineffective hematopoiesis resulting in peripheral blood cytopenias is a hallmark of MDS, and excessive apoptosis of hematopoietic precursors in the marrow appears to be one of the underlying mechanisms. It is possible

## VTD in MDS and MM

**Table 1.** Characteristics of the case reported at diagnosis and during follow-up

	Diagnosis	Month +2	Month +4
Immunoglobulin (g/l)			
Monoclonal IgA (normal: 0.69-3.82)	33.4	8.42	4.51
λ light chain (normal: 2.68-6.38)	28	8.58	5.26
Monoclonal IgG (normal: 7.23-16.85)	2.81	4.68	6.28
Monoclonal IgM (normal: 0.63-2.77)	0.04	0.06	0.54
β <sub>2</sub> -microglobulin (mg/l) (normal: 0.9-3.1)	5.38	2.33	3.58
Bone lesions			
% PC by morphology	12	ND	0
% blast cells by morphology	0.5	ND	85
Flow cytometry results	CD38+, CD56+,	ND	CD34+, CD13+, CD33+, CD64+, CD56+, HLA-DR+
Karyotype	39-44, XY, 5q-, 6q+, 7q+, -13, -16, -17, +m1, +m2 [12]/46, XY [8]	ND	39-44, XY, 5q-, 6q+, 7q+, -13, -16, -17, +m1, +m2 [20]
Treatment	ND	VTD (2 cycles)	ND

PC: plasma cells; ND: not determined/not done.

that VTD therapy promotes apoptosis in both diseases, resulting in a favorable effect on MM and an adverse effect on MDS.

It is unclear to what extent MDS progression in our patient was caused by VTD administration as opposed to the natural progression of the disease. It was of note that VTD was effective in eradicating myeloma cells, but it did not prevent or delay MDS progression to AML. However, the data should be interpreted with great caution as the tumor burden of the two malignancies may have differed significantly.

In summary, this is the first case report of MDS with MM which had rapid evolution of MDS to AML on VTD therapy. More data from more cases are needed, to find the potential utility of VTD therapy in MDS patients.

#### Disclosure of conflict of interest

None.

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