

Acute Leukemia after Multiple Myeloma: A Case Report with Review of the Literature

Beddou G^{1*}, Skalli H¹, Raissi A², Yahyaoui H¹, Benjelloun I¹, Ait Ameer M¹, Chakour M¹

¹Biological Hematology Department, Military Hospital Avicenne, Marrakech, Morocco

²Clinical Hematology Department, Military Hospital Avicenne, Marrakech, Morocco

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*Corresponding author: Beddou Ghita

Abstract

Case Report

The occurrence of acute leukemia after treated multiple myeloma has long raised concerns and has been the subject of several studies which have been based mainly on the link with treatments, mainly those using alkylating agents, but they remain limited due to the small number of patients, insufficient follow-up and limits for detecting second malignant tumors. Although the underlying biological mechanisms of AML after multiple myeloma are unknown, treatment-related factors are believed to be responsible. Recently, an excessive risk of acute leukemia has been found among 5652 patients with monoclonal gammopathy of undetermined significance IgG / IgA (but not IgM) supporting the role of disease-related factors. In addition, there is evidence to suggest that genetic polymorphisms may contribute to a person's susceptibility to future cancers, while the potential influence of environmental and behavioral factors remains poorly understood. This article discusses, through the observation of our patient, the current knowledge concerning malignant tumors after multiple myeloma and gives future directions for efforts to characterize the underlying biological mechanisms, with the aim of increasing survival and minimize the risk of new malignancies.

Keywords: Multiple myeloma, treatments, acute myeloblastic leukemia.

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INTRODUCTION

Multiple myeloma (MM) is a malignant hemopathy characterized by the medullary proliferation of an abnormal plasma cell clone secreting a monoclonal immunoglobulin. It is relatively common in the elderly.

Survival from multiple myeloma has improved significantly in recent years in younger patients. Indeed, multiple myeloma has seen more remarkable advances in treatment and patient outcomes than other cancers in the past decade. With improved survival, a new clinical challenge has emerged which is the risk of second malignancies. This tendency to increase these secondary hemopathies has been observed in other cancers with therapies and favorable results.

OBSERVATION

The 62-year-old patient followed for multiple myeloma for 6 years, the diagnosis of myeloma was retained before infiltration of the bone marrow by malignant plasma cells (75%), hypercalcemia at 3.98 mmol / l, anemia at 8 g / dl, vertebral compaction. At EPP, a monoclonal gamma peak confirmed at

immunofixation was objectified. The patient was on CTD protocol: cyclophosphamide thalidomide dexamethasone, and biphosphonate, with good clinical and biological progress and was declared in remission in early 2019.

In December 2019 the patient presents to the emergency room for deterioration in general condition. On examination, he presented with an intense mucosal and skin rash and petechiae. On the blood count : leukocyte at 9.28×10^3 without leukocyte formula, anemia at 7.3 g / dl normochromic normocytic and platelets at 7×10^3 with the presence of the Blasts alarm The blood smear found 31% blasts, 9% PNN, 35% lymphocytes, 22% monocytes, 3% plasmacytes and 5/100 GB of circulating erythroblasts.

The myelogram showed a very rich marrow invaded by 63% of blasts with a cytological appearance in favor of AML with the presence of dystrophic plasma cells at 5% and posed the diagnosis of acute myeloid leukemia of the myelomonocytic type (AML4 of the French-American and British classification). Immunophenotypic analysis of blast cells showed positive labeling for CD13, CD14, CD15, and CD33. A

karyotype found complex cytogenetic anomalies (4 mitoses / 20) of poor prognostic value.

DISCUSSION

Acute myeloblastic leukemia (AML) following MM treatments have been described for several decades [1, 2].

In the late 1960s, on the basis of a small number of patients, the association between multiple myeloma and leukemia was first described [3, 4]. This was later confirmed by numerous case reports. Risk quantification was impossible until follow-up reports from several hundred myeloma patients treated with alkylating agents, particularly with melphalan, were described. The overall incidence of acute leukemia in these patients was 100 ± 200 times greater than that expected in the general population.

In 1979, on the basis of a clinical trial, including 364 patients with multiple myeloma, Bergsagel et al. Have a higher incidence than expected of all forms of acute leukemia in patients treated with low dose melphalan containing combinations of alkylating agents [5].

Although the use of low doses of melphalan decreased considerably with autologous stem cell transplantation (ASCT) in the late 1980s, melphalan combinations continue to be used in patients not eligible for ASCT [6].

After the introduction of high-dose melphalan / ASCT, several studies have focused on the relative contribution of myeloablative therapy in the development of myelodysplastic syndrome (MDS)/ acute myeloblastic leukemia (AML).

Over the past decade, agents with new mechanisms of action (such as thalidomide, bortezomib, and lenalidomide), and the continuous improvement of therapeutic support measures have further improved response rates, survival without progression and overall survival in multiple myeloma. Recently, there have been reports of an increased risk of second malignancies, mainly MDS / acute leukemia, with lenalidomide, in several patients with myeloma.

In a recent study, Cuzick *et al.*, reported a link between the duration of treatment and the subsequent risk of developing leukemia [7]. In this study, the cumulative dose was administered 3 years before the onset of leukemia; duration has been reported as the most important determinant of risk. However, this association has not been verified in all studies; For example, a Finnish retrospective cohort study found no significant association between the duration of cumulative doses and the risk of developing AML after multiple myeloma [8].

Govindarajan et al compared 2 groups of patients with different exposure to alkylating agents before transplantation. Group 1 had received only one standard alkylating treatment cycle and Group 2 had significantly prolonged exposure to chemotherapy, including alkylating before transplantation. Both groups were treated with a high dose cyclophosphamide (CTX) cycle [9].

Despite a longer follow-up (36 months vs 29 months; P. 05), none of the patients in group 1 developed AML, while 7 patients in group 2 had AML [9]. Other studies have also demonstrated that conventional chemotherapy before AST is a more likely contributing factor for MDS / acute leukemia.

Although known for several decades, precise estimates of the incidence and pathogenesis of acute post-myeloma leukemia are lacking and should be interpreted with caution. Most previous studies are small due to the small number of patients and inadequate follow-up. Largely due to insufficient data and a small number of studies, it seems reasonable to consider that the development of leukemia or other malignant tumors after multiple myeloma is most likely a multifactorial process.

Contributing factors likely include various treatments for multiple myeloma, factors related to multiple myeloma, factors related to the host, as well as environmental and behavioral factors. Historically, efforts have focused on the role of factors related to treatment, such as alkylating agents. However, the role of the various factors remains largely unexplored. For example, based on small numbers of patients, there are indications that genetic polymorphisms of the host may play a role in the pathogenesis of second malignant tumors [10].

In addition, recent data suggest that IgG / IgA in MGUS patients may also be at increased risk for AML / MDS [11]. These results confirm the role of host and disease factors and, if validated in larger studies, they pave the way for future investigations designed to define the underlying molecular mechanisms. Other factors unrelated to treatment, such as environment and behavior, also remain poorly understood.

CONCLUSION

In the context of the increase in overall survival in multiple myeloma and the recently reported increase in second malignancies associated with the use of lenalidomide, it is imperative that we re-address the association between multiple myeloma and leukemia, which was first reported in the late 1960s [12, 13].

To this end, collaborative efforts are necessary to better study the characteristics of patients who develop a second malignant tumor after multiple myeloma. Such efforts would allow us to better define

the role of different factors in order to allow us to identify high-risk and low-risk patients, and to adapt therapy, with the aim of increasing survival and minimizing the risk of a second malignant tumor for the patient.

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