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Case Report

First reported case of secondary mixed phenotype acute leukemia after multiple myeloma

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Abstract: In recent years the outcome of patients with multiple myeloma (MM) has significantly improved, due to new drugs. However, some agents, i.e. the alkylating drug melphalan, can be associated with an increased incidence of secondary malignancies. Myelodysplastic syndromes and acute myeloid leukemia are reported in the literature, and rarely acute lymphoblastic leukemia. Here we describe a unique case of a 56-years old female patient affected by MM since 2015 in complete remission after autologous stem cell transplant and in lenalidomide maintenance, who developed 2 years later mixed phenotype acute leukemia (MPAL). The patient, refractory to both lymphoblastic and myeloid acute leukemia regimens, achieved complete remission with bi-specific anti-CD19/anti-CD3 monoclonal antibody blinatumomab and with hypomethylating agent azacytidine plus the BCL-2 inhibitor venetoclax. She then underwent hematopoietic stem cell transplantation from HLA-identical sibling donor and she is still in complete remission after 9 months. To the best of our knowledge, there are no cases in the literature describing MPAL after autologous transplant for MM. Our patient was treated with blinatumomab and venetoclax and achieved complete remission 9 months from allogeneic transplant. The mechanism underlying the development of MPAL is not completely understood and therapies are still lacking. In this context the combination of blinatumomab, azacytidine and venetoclax successfully used in this patient may provide food for thought for further studies in this rare setting of patients.

Keywords: Mixed phenotype acute leukemia, multiple myeloma, secondary acute leukemia

Introduction

In recent years the outcome of patients affected by multiple myeloma (MM) has improved, with a median survival of 8 years [1]. Despite this, MM patients are at higher risk of second primary malignancies (SPMs) because of patient susceptibility and the use of alkylating based chemotherapy [2]. Better survival is related to the use of autologous stem cell transplantation (ASCT), 'novel agents' such as proteasome inhibitors (bortezomib, carfilzomib), and immunomodulatory drugs (thalidomide, lenalidomide). However, this led to an increased incidence of SPMs [3]. SPMs development in patients with MM is multi-causal. Older age and male sex have been described to be risk factors for SPMs in different studies [4-6]. Nonetheless, age <65 years, and female sex have been associated with an increased risk of leukemia [7]. Also, genetic alterations related to environmental factors may predispose to SPMs [8, 9]. MM itself, regardless of therapy received, has been associated with an increased risk of SPMs, especially acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [10-12]. Also, the use of alkylating agents has been linked to an increased risk for therapy-related myeloid neoplasms (t-MNs), including AML and MDS [13, 14]. And even the use of the immunomodulatory drug lenalidomide has been recently related to an increased incidence of SPMs in both transplant-eligible and transplant-ineligible patients, especially when administered with oral melphalan [15-17]. In a recent meta-analysis of seven randomized controlled clinical trials in which lenalidomide was used as first line therapy, the incidence of SPMs at 5 years was 3.1% and 1.4% in the lenalidomide vs non-lenalidomide group, respectively. Interestingly, cases of acute lymphoblastic leukemia (ALL) have rarely

Table 1. Type of therapy and responses according to MM and ALL diagnosis

Type of disease	Therapy	Response
MM (Oct. 2015)	INDUCTION: 4 cycles of KRD→(carfilzomib 36 mg/m^2 on days 1, 2, 8, 9, 15, 16; dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg on days 1-21; 28-day schedule) ASCT (Mel 200) CONSOLIDATION: 4 cycles of KRD→(carfilzomib 36 mg/m^2 on days 1, 2, 8, 9, 15, 16; dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16; lenalidomide 25 mg on days 1-21; 28-day schedule) MAINTENANCE: Lenalidomide 5 mg day	sCR (Oct. 2016) sCR (Oct. 2016-Oct. 2018)
ALL (Sept. 2019)	INDUCTION: prednisone 20 mg/m^2 orally days -5→-1; cyclophosphamide 200 mg/m^2 IV on days -3→-1; idarubicin 9 mg/m^2 IV on days 1-2; vincristin 1.4 mg/m^2 IV days 1, 8, 15, 22; peg-asparaginase 1000 IU/m^2 IV day 10; dexamethasone 5 mg/m^2 twice daily 1-5, 15-19; G-CSF 5 mcg/kg SC from day 5 to recovery + CNS prophylaxis REINDUCTION: HAM: high-dose cytosine arabinoside 3000 mg/m^2 twice daily, days 1-4 and mitoxantrone 10 mg/m^2 on days 2-5 Blinatumomab 9 mcg IV days 1-7, then 28 mcg IV on days 8-28 Venetoclax (with a rump-up schedule) 400 mg/day + azacytidine 75 mg/m^2 Allo-RIC (Feb. 2020): thiotepa 270 mg days -6 and -5, busulfan 150 mg days -4, -3, fludarabine 75 mg days -4 to -2 (Cells given: 4.74 × 10^6 CD34/kg + 2.83 × 10^8 CD3/Kg from a peripheral blood graft)	PR PR CR CR CR

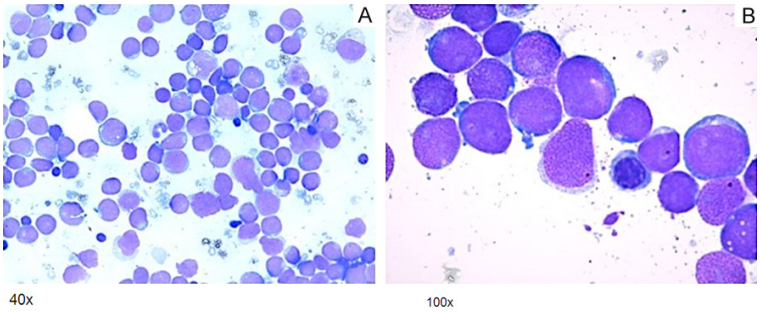

Figure 1. Morphology of bone marrow aspirate (May-Grunwald-Giemsa stain). A variation can be seen in blast size with a majority of relatively small blasts and less frequent larger blasts at 40 × (A) and 100 × (B).

been observed after lenalidomide treatment [16-19]. However, cases of mixed-phenotype acute leukemia (MPAL) in MM patients have never been reported in the current literature. Here we report the first case of a patient with MM who was diagnosed with MPAL during lenalidomide maintenance therapy after ASCT.

Case report

A 57-year-old female was referred to the hematologist by the Emergency room of our hospital in October 2015 because of multiple osteolytic lesions after an X-ray done for diffuse lumbar and ribs pain. Bone marrow examination and biochemicals confirmed the diagnosis of IgG lambda multiple myeloma ISS (International Staging System) stage 3, Durie-Salmon (DS) stage IIIA, with 40% monoclonal plasma cells and t(11;14) after fluorescent in situ hybridization (FISH) done on CD38 purified plasma cells. The patient was treated with KRd (carfilzomib/lenalidomide/dexamethasone) (**Table 1**) after ethical committee approval and patient informed consent were obtained. Carfilzomib was given in four 28-day cycles 36 mg/m^2 associated with dexamethasone, 20 mg (both at days 1, 2, 8, 9, 15, 16), and lenalidomide, 25 mg (days 1-21). The patient subsequently received autologous stem cell transplant in February 2016. Four additional consolidation cycles of KRD were given and maintenance therapy with lenalidomide 5 mg was initiated (from October 2016 to October 2018). During this period the patient remained in stringent complete response according to IMWG criteria [20] until September 2019, when routine blood tests revealed a decreased platelet (PLT) count of 38 × 10^3/μL, hemoglobin (Hb) 12.5 g/dL, and white blood cell (WBC) 6430/μL. The blood-smear showed 18% of blasts with increased nuclear-cytoplasmic ratio, prominent nucleoli, and basophilic cytoplasm. Bone Marrow aspirate showed hypercellularity, with 100% of blasts in the bone marrow (**Figure 1**). Flow-cytometry confirmed the presence of bi-phenotypic blasts positive for CD34 (99%), CD13 (28%), CD19 (99%), CD22^{low} (100%), HLADR (99%), CD9 (46%), CD123 (99%), CD58 (99%), CD81 (88%), CD66c (98%), CD24 (76%), CD38 (99%), CyCD22^{low} (100%), TdT (97%), MPO (11%) and Bcl-2 protein was high express (mean fluorescence index of 17.6 and mean fluorescence index of lymphocytes of 16.8). Results were consistent with mixed phenotype acute (MPAL) leukemia B/myeloid, not otherwise specified (NOS) (**Figure 2**). Cytogenetics revealed a normal karyotype (46, XX [20/20]) with negative FISH examination for mixed-lineage leukemia gene (*MLL)* rearrangement and *BCR/ABL* fusion gene, and molecular analysis was negative for *FLT-3, NPM1, Wt-1* alterations. However, 4 signals for chromosomes 9, 11, and 12 were detected in 10% and 20% of cells respectively, by FISH analysis, compatible with two small tetrasomy clones. The serum immunofixation was negative for the monoclonal component. Cerebrospinal fluid (CSF) evaluation did not show leukemia involvement. She received induction chemotherapy with ALL-pediatric oriented chemotherapy with prednisone (20 mg/m^2 orally days -5→-1), cyclophosphamide (200 mg/m^2 intravenously, IV on days -3→-1), idarubicin (9 mg/m^2 IV on days 1-2), vincristine (1.4 mg/m^2 IV days 1, 8, 15, 22), peg-asparaginase (1000 IU/m^2 IV day 10), dexamethasone (5 mg/m^2 twice daily 1-5, 15-19), G-CSF (5 mcg/kg subcutaneously, SC from day 5) [21], obtaining a partial remission (residual bone marrow aspirate blasts 10%, at flow cytometry 3%). A second induction chemotherapy with high-dose cytosine arabinoside (3000 mg/m^2 twice daily, days 1-4) and mitoxantrone (10 mg/m^2 days 2-5) according to the HAM scheme was attempted. The subsequent assessment showed an incomplete blood recovery (WBC 1.5 × 10^3/μL; Hb 9 g/dl; PLT 26 × 10^3/μL), a bone marrow morphological partial remission (10%

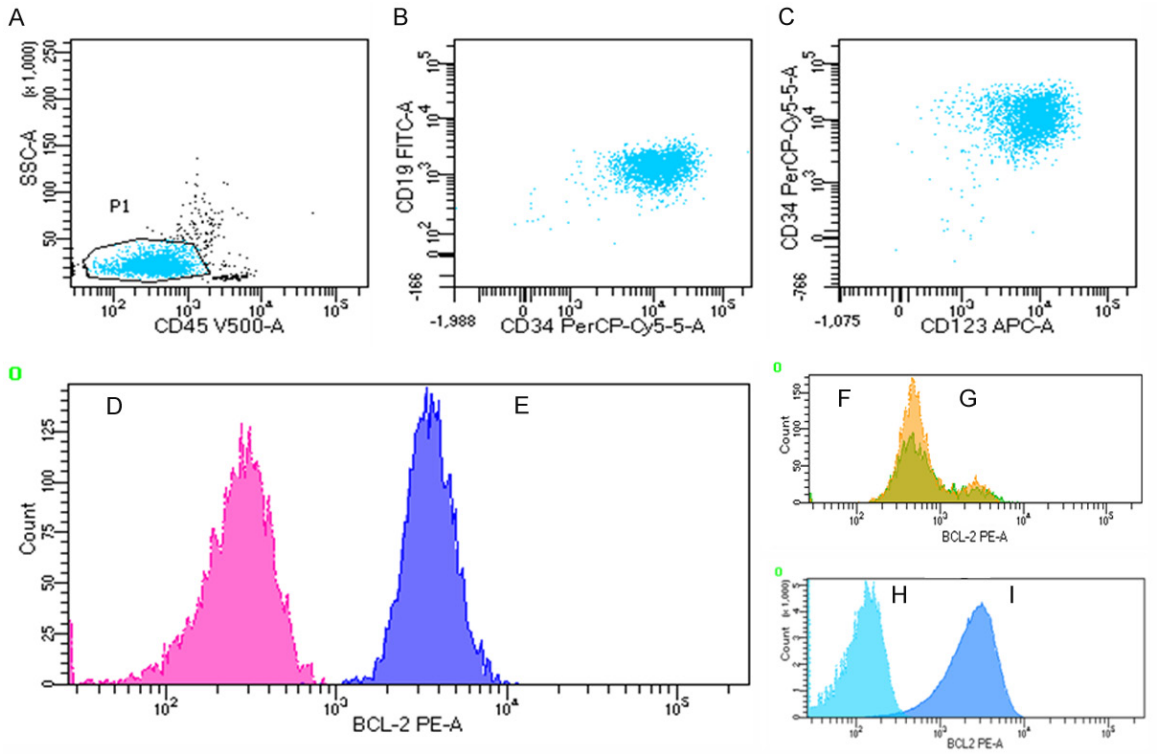

Figure 2. MPAL flow cytometric immunophenotyping. Expression of BCL-2 protein by flow cytometry in neoplastic cells. Identification of population CD45 negative with low SSC (A); all cells express CD34 and CD19 antigens (B) and CD123 antigen (C); histograms of isotypic control and (D) BCL-2 protein (E). BCL-2 protein expression an isotypic control in granulated cells (F and G) and lymphocytes (H and I).

blasts), and cytofluorimetric minimal residual disease (MRD) of 0.45%. Therefore, given the expression of CD19 on blast cells, the patient received one cycle of bi-specific anti-CD19/anti-CD3 monoclonal antibody blinatumomab at a standard dose of 9 mcg IV on days 1 to 7 and 28 mcg IV on days 8 to 28, obtaining for the first time a morphological complete remission with a cytofluorimetric MRD of 0.0433%. Afterwards, as the expression of BCL-2 on blast cells was also confirmed, a short-term venetoclax 400 mg/day plus the hypomethylating agent azacytidine 75 mg/m^2 was given to the patient as bridge to allogeneic transplant. Pre-transplant evaluation confirmed complete remission with a 1 log further reduction of flow MRD (0.008%). From the diagnosis, she also received 5 intrathecal medications as CNS prophylaxis with methotrexate (12.5 mg), cytarabine (50 mg), and dexamethasone (4 mg). The patient underwent a matched sibling donor allogeneic hematopoietic stem cell transplantation (HSCT) with reduced-intensity conditioning (thiotepa, 270 mg days -6 and -5; busulfan, 150 mg days -4 and -3 and fludarabine, 75 mg days -4 to -2) and received 4.74 × 10^6 CD34/kg and 2.83 × 10^8 CD3/Kg from a peripheral blood graft. At last follow up, 9 months after HSCT, the patient maintains CR for MPAL and MM and no graft versus host disease.

Discussion

We report here a unique case of refractory MPAL treated successfully with blinatumomab, venetoclax, azacytidine and allogeneic transplantation. At present, to the best of our knowledge, there are no cases MM reported in the literature who have developed this type of leukemia. The patient had a history of multiple myeloma, with long exposure to the immunomodulating agent lenalidomide. She also received high doses of melphalan as conditioning autologous transplant, that may have contributed to the development of leukemia. Acute myeloid leukemia and myelodysplastic syndromes are the hematologic neoplasms more frequently seen in a post-transplant setting, but this patient was diagnosed with a leukemic form which is unusual in this context, and itself is already rare. Indeed, mixed phenotype acute leukemia, firstly named leukemia of "am-

Table 2. Cases of acute leukemias following lenalidomide maintenance for multiple myeloma

Patient	MM treatment	Maintenance lenalidomide dose	Diagnosis of secondary ALL, time since MM	Comments
62-year-old female	Bortezomib, dexamethasone, vincristine, carmustine, melphalan, cyclophosphamide, prednisone, doxorubicin, dexamethasone, lenalidomide, ASCT	10 mg daily	ALL, 20 months	induction therapy for adult ALL (not specified), died for infection
66 old man	Bortezomib, dexamethasone vincristine, pirarubicin, dexamethasone and melphalan regimen	10 mg daily for 2 months then thalidomide	ALL, 38 months	Death after 8 months with no response to induction therapy
72-year-old male	vincristine, doxorubicin, and dexamethasone; lenalidomide-dexamethasone	unknown	ALL and myelofibrosis	Hyper-CVAD, POMP maintenance. CR for 26 months, then relapse
age 65 years or older	Melphalan, prednisone, lenalidomide	10 mg daily	ALL, unknown	Not specified
59-year-old man	Lenalidomide, bortezomib, dexamethasone, melphalan, ASCT	Unknown	ALL, 33 months	alive > 1 y after allo-SCT in CR
34-year-old man	Dexamethasone, thalidomide, lenalidomide	5 mg TIW	ALL, 39 months	CALGB 8811 protocol, dead after 1 month from diagnosis
53-year-old man	Lenalidomide, bortezomib, dexamethasone, melphalan, ASCT	25 mg daily	ALL, 92 months	ALLOSCT, > 1 year in CR
65-year-old female	vincristine, pirarubicin, dexamethasone, melphalan	10 mg daily (then thalidomide)	ALL, 34 months	Refused treatment, dead
56-year-old female (present case)	Carfilzomib lenalidomide dexamethasone, ASCT	5 mg daily	MPAL, 11 months	prednisone cyclophosphamide idarubicin peg-asparaginase dexamethasone HDAC, mitoxantrone, blinatumomab, veetoclax + azacytidine, ALLOSCT, 9 months in CR

Adapted from Khan et al. [46].

bigous" lineage almost 40 years ago, is a rare disease (3% of acute leukemias), carrying a worse prognosis [22-24].

The immunophenotypic markers are multilineage, with a mixed expression of B, T, and myeloid antigens [25-27]. MPAL is characterized by a higher risk of death than ALL and AML [28]. Cytogenetic and molecular features are poorly characterized, however it is important to rule out the presence of the chromosome Philadelphia, resulting from translocation 9;22 [29]. Since MPAL is a rare disease, there are few therapeutic data in this regard, with many retrospective studies addressing an ALL-regimen followed by consolidation chemotherapy and/or HSCT as the best therapeutic option [30-34]. The currently available data seem to establish that combining AML/ALL type of therapies did not induce a higher remission rate and worse survivals and increased toxicity were present, when compared with AML or ALL approaches [29, 35]. Our patient failed an ALL induction therapy and achieved only a partial remission following a salvage regimen like HAM that has shown effectiveness both in refractory ALL and AML. Quite unexpectedly, the sequential use of the bispecific anti CD19/CD3 monoclonal antibody, azacytidine and BCL-2 antagonist was very effective in this rare leukemic form allowing the patient to achieve a molecular complete response and to proceed to allogeneic transplant. Two cases in the literature have been reported on the effectiveness of blinatumomab in MPAL leukemia [36-38].

In our patient, the development of MPAL could be related to the combined effects of lenalidomide and alkylating agents. Recently, the "Nemesis" study found that the cumulative incidence of developing SPM is 3.5% [39], which is similar to the incidence reported in 2 previous studies (3% and 4.4%, respectively) [40, 41], while the incidence of secondary leukemia in MM patients ranges from 0.7% to 25% [42]. The median time to the diagnosis for secondary hematologic malignancies is 24 months, thus affecting life expectancy and quality of life [16, 43]. Among acute leukemias, the development of myeloid forms seems to be slightly more frequent than ALL, whose frequency is reported in a very low percentage [44].

In a recent review of a case series of 7 MM patients receiving lenalidomide therapy who developed secondary ALL (**Table 2**), the authors hypothesized it could be duration related rather than dose-related [18]. Lenalidomide could promote myelosuppression and select abnormal clones, leading to malignancy [45]. The drug can also affect in particular B cells, reactivating the Epstein-Barr virus lytic cycle in resting memory B cells, and contributing to increased immunosuppression [46]. Few cases of secondary Hodgkin's lymphomas have been reported related to lenalidomide maintenance after ASCT [47]. Among lenalidomide effects, one mechanism is the alteration of ubiquitination [48-50], leading to the expansion of the regulatory T cells (Treg) [51].

Treg could potentially promote immune tolerance towards any abnormal clonal expansion. However, the action of IMiDs on Treg in myeloma patients is more complex and seems controversial [52].

Conclusion

This is the first report of a mixed phenotype acute leukemia arising in a patient affected by multiple myeloma in complete remission. A possible mechanism related to the development of this disease may be referred to the combined use of lenalidomide and melphalan. Although rare, increased awareness of this secondary malignancy may allow for a careful study of these patients. Further studies are needed to investigate the complexity of MPAL. The combination of blinatumomab, venetoclax and hypomethylating agents successfully used in this patient may provide food for thought for alternative therapeutic approach in this rare setting of patients.

Disclosure of conflict of interest

None.

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