A case of synchronous dual hematological malignancy: effects of multiple myeloma therapy on essential thrombocythemia and vice versa

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Abstract

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Case Report

A case of synchronous dual hematological malignancy: effects of multiple myeloma therapy on essential thrombocythemia and vice versa

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Short Title: Synchronous MM and ET

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Abstract

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anti-myeloma therapy. Treatment for MM had no effect on ET; concomitant ET did not decrease the efficacy of anti-myeloma therapies in this frail patient.

Introduction

Dual malignancies occurring in the same patient are reported in the literature [1]; however, dual hematological malignancies (DHMs) are recognized less frequently [2-5] and are likely underreported [6]. DHMs can been classified as either synchronous (SDHMs), when occurring within six months of diagnosis of the first malignancy, or asynchronous when occurring later [1]. Using a more restrictive cut off of one month, we had earlier reported a 1.5% incidence of SDHMs in patients referred to our cancer center [6]. The detection of DHMs may be an incidental finding during routine bloodwork or during investigation of discrepant clinical and laboratory findings [6]. The observed underreporting, and potential under detection, of SDHMs may be because of masking from the primary malignancy [6]. DHMs involving essential thrombocythemia (ET) and multiple myeloma (MM) are quite uncommon, and most cases report MM developing years after ET diagnosis. The occurrence of these two malignancies synchronously is extremely rare. We report a case of concurrent MM and ET in a frail elderly patient. We review the literature, discuss possible mechanisms, and present potential challenges in the management of such patients.

Patient Information/ Clinical Findings

An 86-year-old female presented to the emergency in May 2016 with confusion, hypercalcemia, and acute kidney injury. Her past medical history included hypertension, hyperlipidemia, and osteoporosis. She was brought to the clinic on a stretcher with an Eastern Cooperative Oncology Group (ECOG) status of 4. On examination, she was disoriented and had tenderness along her left rib cage. Investigations showed hemoglobin (Hb) 82 g/L, macrocytosis (MCV 134), rouleaux, WBC 4.2 x10^9 with normal differential, and platelets 226 x 10^9/L (shown in Fig. 1A). Chemistry showed total protein 99 g/L, albumin 26 g/L, calcium 3.15 mmol/L, and creatinine clearance 17 mL/min. Total IgG was elevated (45.9 g/L) with reciprocally decreased IgA and IgM. Monoclonal Protein (MP) was 41.8 g/L. Free Light Chain (FLC) lambda was elevated (9,050 mg/L). Skeletal survey showed osteopenia and a T12 vertebral compression fracture. Bone marrow (BM) examination showed infiltration by plasma cells comprising up to 90% of nucleated cells including occasional binuclear and atypical plasma cells (PC) (shown in Fig. 1B). The PC were kappa restricted and had strong cytoplasmic CD138+ expression (shown in Fig. 1C). Erythroid and megakaryocytic maturation was reduced but normal morphologically.

Diagnostic Assessment/Therapeutic Intervention

At that stage the patient was presenting with the classical picture of FLC lambda and IgG lambda multiple myeloma (MM), standard risk. Fluorescence in situ hybridization (FISH) was positive for monosomy 13/13q deletion and no high risk abnormalities, like del(17p) or t(4;14) and/or t(14;16), were found. Revised International Staging System was II. Since her platelet count was normal, no work up for myeloproliferative neoplasms was done.

She started MPV (Melphalan–Prednisone–Bortezomib) treatment with Darbopoietin support in June 2016. By October 2016, her Hb improved to 132 g/L and FLC decreased to 9.7 mg/L. She reached stringent complete remission (CR) with no MP detected on serum protein electrophoresis (SPEP) or immunofixation (IFE). We noticed her platelet counts increase to 514 x10^9/L in July, 810 x10^9/L in September, and to 1,518 x10^9/L in October.

Due to the appearance of unexpected thrombocytosis, we first ruled out infections and iron deficiency. The platelet count was unusually high for secondary causes for thrombocytosis, thus we initiated work up for myeloproliferative neoplasms. JAK2 mutation was negative, but she was found to have a mutation in exon 9 of Calreticulin (CALR). We concluded that she had concomitant CALR-positive ET. Based on an International Prognostic Score for Essential Thrombocytopenia score of 4, she had high risk ET. Due to classical ET presentation and the patient's preference, we omitted repeated bone marrow examination. Aspirin and Hydroxyurea (HU) were added to MPV, stabilizing her platelet counts (300x10^9/L). As this

second diagnosis occurred within 5 months of diagnosis of the first malignancy, we updated her diagnosis to a synchronous dual hematological malignancy (SDHM): MM and ET, initially masked by marrow infiltration by PC.

She finished MPV in April 2017. By August 2018, her platelets were 388 x10^9/L; she relapsed, with FLC climbing to 1,130 mg/L, MP 23.9 g/L, and Hb dropping to 104 g/L. HU was held and she was started on second-line Lenalidomide-Dexamethasone (Ld) treatment for MM. Upon achieving a second CR, her platelet count increased to 500 x 10^9/L and HU was restarted. In March 2019, her MM progressed again with FLC increasing over 600 mg/L, and MP 17.0 g/L. She developed new anemia (Hb 114 g/L) and thrombocytopenia (platelets 118 x 10^9/L). Once again, HU was held. She was started on third-line anti-myeloma therapy with DVd (Daratumumab-Bortezomib-Dexamethasone) in April 2019. FLC decreased to 11.5 mg/L, MP was down to 0.2 g/L, Hb increased to 120 g/L, and platelets increased (580 x10^9/L). She attained third remission and we re-started HU. After the 7th cycle with DVd, however, her FLC increased again to 255 mg/L, MP was 6.9 g/L, and Hb decreased to 110 g/L. HU was put on hold and platelets remained low-normal (154 x10^9/L). In October 2019 she started fourth-line therapy with PCd (Pomalidomide-Cyclophosphamide-Dexamethasone), and she reached CR with no measurable MP and normalization of FLC kappa (6.6 mg/L) in December 2019. Platelet count was 247 x 10^9/L. She was in remission until June 2020 when she progressed to PC leukemia and passed away. FLC and platelet counts dynamics over the course of disease and treatment is shown in Figure 2.

Discussion/Conclusion

SDHMs are suspected if certain clinical, hematological, or biochemical features cannot be explained by the primary malignancy alone. These cases can be challenging to diagnose and treat and warrant additional attention and investigation. Table 1 summarizes case reports of synchronous ET and MM [7-12]. The median patient age was 59 years, with equal gender distribution (five males and three females). The median platelet count was 835 x 10^9/L. Plasma cells in bone marrow ranged from 11.5% to 90%, as well as one patient who had only 6% PCs but presented with a plasmacytoma. Molecular markers were only reported for three cases and were all JAK2 positive. ET and MM were diagnosed concomitantly in all except one, in which ET diagnosis preceded that of MM by one month.

There are more reports of asynchronous MM and ET, as summarized in Table 2 [13-24]. The median patient age was 67 years, with 9 males and 5 females. The median platelet count was 1,065 x 10^9/L. Bone marrow PCs ranged from 24% to 100%. Molecular markers were only reported for five of the cases: three were JAK2 positive while two were JAK2 negative. In all cases, ET preceded MM with a median of 4.5 years between diagnoses.

Reports prior to 2011 did not describe JAK2 status or calreticulin mutations. Additionally, none of the previous reports of synchronous MM and ET had simultaneous treatment for both malignancies, as was required in our case. Although the exact mechanism of such SDHMs is not clearly understood, there are several possible reasons. Firstly, a common trigger at the stem cell level may lead to their differentiation into myeloid (ET) and lymphoid (MM) cells [12]. Secondly, the two malignancies may arise from separate malignant clones at different differentiation levels [16]. Alternatively, therapy for one malignancy may cause or trigger development of the second malignancy [25], however, this is unlikely to be the case in SDHMs, as in our patient. Additionally, it has been suggested that Interleukin-6 may cause reactive thrombocytosis via stimulation of thrombopoietin, and may precipitate synchronous development of ET [26]. It is also possible, however, that the occurrence of the two malignancies was purely coincidental. MM is a slowly progressing malignancy, with an average time gap of 163 days from symptom onset to diagnosis [27], so it may have been present subclinically for some time in our patient before its diagnosis meaning that these malignancies may not necessarily have been synchronous. Due to the concomitant development of ET and MM in our patient, it is likely that BM infiltration by PC suppressed excessive megakaryopoiesis and thus masked ET. With restoration of hematopoiesis by anti-myeloma therapy, the patient developed thrombocytosis. In such cases when clinical or biochemical parameters cannot be explained by the primary malignancy alone, it is important to consider DHMs.

In managing such patients, one needs to treat the malignancy that has a more aggressive, life-threatening course or the potential to transform into acute leukemia. In our case, we first treated for MM. Unexpected extreme thrombocytosis prompted addition of cytoreductive therapy for ET. Additionally, therapy for DHMs needs to balance disease control, the patient's condition, and BM capacity. We did not observe any effect of treatment for MPV, Ld or Daratumumab on ET. With the fourth-line PCd, the patient had normalization of platelets, but not to the level of thrombocytosis; possibly due to "tired bone marrow" with decreased capacity to produce excess platelets or due to anti-platelet effects of PCd. Similarly, therapy with HU for ET did not have any effect on the course of MM. Duration of response with all therapies in our patient was comparable to that of previously reported patients with MM alone. Despite our patient's age, comorbidities, and combination of treatments, she tolerated multiple lines of treatment well for both malignancies and achieved CR.

In conclusion, synchronous MM and ET is rare. BM suppression by MM can mask thrombocytosis at diagnosis. Restoration of hematopoiesis due to anti-myeloma therapy may uncover ET. Therapy of MM does not affect ET, except probably use of PCd. Frequent monitoring of both malignancies is important, as drops in blood counts could be a result of either cytoreductive therapy or MM relapse. Presence of concomitant ET did not decrease efficacy of sequential anti-myeloma therapies in our elderly and frail patient.

Statements

Statement of Ethics Ethical approval is not required for this study in accordance with our local guidelines. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed Consent for Publication was obtained from the patient's daughter (next-of-kin) for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.K., R.P., and R.K. wrote and reviewed the manuscript. All authors approved the final version to be published and agreed to act as guarantors of the work. .

Data Availability Statement

All data that support the findings of this study are included in this article

Supplementary Material The CARE Checklist has been completed by the authors for this case report, attached as supplementary material

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Figure Legends

Fig. 1A. Peripheral blood film showing multiple rouleaux, morphologically normal WBC and platelets. May-Giemsa, x100 objective.

Fig. 1B. Bone marrow aspirate with numerous plasma cells, comprising over 90% of bone marrow cells, reduced erythopoiesis, granulopoiesis and thrombopoiesis. Plasma cells contain Dutcher bodies and Russell bodies. H&E, x200 objective.

Fig. 1C. Strong expression of CD138 on plasma cell surface. Clot section, H&E, x200 objective.

Fig. 2. Graphical changes over time in patient's, hemoglobin, platelet counts, and affected free light chain over the course of disease and anti-myeloma therapy. Hb, Hemoglobin (g/L); Plt, platelet count ($x10^9$/L), FLC, serum free light chain (mg/L); MPV, Melphalan, Prednisone, Velcade (Bortezomib); Ld, Lenalidomide and dexamethasone; DVd, Daratumumab, Velcade (Bortezomib), dexamethasone; PCd, Pomalidomide, Cyclophosphamide, dexamethasone; Id, Ixazomib, dexamethasone.