CLINICAL VIGNETTE

Evolution of Multiple Myeloma to B-cell Acute Lymphoblastic Leukemia

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Case

An 89-year-old female with a 4-year history of smoldering multiple myeloma (SMM) presented with persistent fatigue after a motor vehicle accident one month prior. She also noted 3 days of watery diarrhea and weakness. Her vital signs were within normal limits, and she had no abdominal tenderness nor lymphadenopathy on exam. Six months prior her WBC was 3.4 x 10^3 /µl with hemoglobin 11.0 g/dl, hematocrit 34.0% and platelet count of 136 x 10^3 /µl. Her current WBC was 28.09 x 10^3 /µl with hemoglobin 7.4 g/dl, hematocrit 23.7% and platelet count of 63,000 x 10^3 /µl. The day after visiting her primary care physician, she was seen by her hematologist who noted her peripheral blood smear had approximately 80% blasts, confirming acute lymphoblastic leukemia (ALL) which prompted hospital admission. Empiric treatment with vincristine and prednisone was begun. Additionally, she was started on allopurinol for tumor lysis syndrome prophylaxis, and atovaquone 750 mg twice daily, levofloxacin 500 mg daily, acyclovir 400 mg twice daily, and posaconazole 300 mg daily for prophylaxis for infection. Bone marrow biopsy showed clonal evolution of her prior SMM to B-cell acute lymphoblastic leukemia (B-ALL), involving greater than 90% of marrow cells. Daratumumab IV infusion monotherapy began on hospital day 4 for simultaneous multiple myeloma (MM). The patient was discharged home with a 4-day follow-up with her hematologist to continue weekly outpatient vincristine and daratumumab. One week after being seen by her outpatient hematologist, she developed recurrent generalized weakness and was admitted for sepsis from pneumonia and hyponatremia with volume overload. She developed atrial fibrillation with rapid ventricular response and transferred to the ICU with hypotension and neutropenia. Vincristine was discontinued and cefepime was continued. Further findings supported acute heart failure: B-type natriuretic peptide was 491 pg/mL, serum osmolality was 270 mOsm/kg, bilateral pleural effusions were present, and urine sodium was less than 20 mEq/L. She developed oliguria with worsening AKI despite dopamine support. With worsening clinical condition transitioned to comfort care and died in the hospital.

Four years prior to her B-ALL diagnosis, the patient presented with abdominal pain. Abdominal and pelvic CT showed marked osseous demineralization and small hypodense lesions in the spine and pelvis consistent with MM. Serum protein electrophoresis (SPEP) showed an M spike of 2.7 g/dL, serum IgG of 3350 mg/dl, IgA of 23 mg/dl, and IgM of 24 mg/dl with free serum lambda light chains of 298, kappa light chains of 7 mg/dl, and hemoglobin of 10.8 g/dl. She was started on weekly bortezomib with dexamethasone, as well as lenalidomide maintenance for 3 months. Six months after initial diagnosis, she continued lenalidomide maintenance with stable SMM for the next 3.5 years, about 6 months before her B-ALL diagnosis.

Discussion

Multiple myeloma ccounts for approximately 17 percent of all hematologic malignancies. It affects primarily of older adults with a median age of diagnosis of 66 years.[1,2] SMM is distinguished from MM by meeting two criteria: 1) a serum monoclonal protein greater than or equal to 3 g/dL or urinary monoclonal protein greater than or equal to 500 mg per 24 hours and/or 10-60% bone marrow plasma cells and 2) absence of myeloma-defining events or amyloidosis.[3] The majority of SMM patients progress to symptomatic MM or AL amyloidosis with a median time to progression of 4.8 years.[4] Our patient was followed closely with routine SPEP monitoring but her disease was unusual progressing from SMM with a subsequent clonal evolution to B-ALL. For the majority of her disease course, our patient lacked most of the typical CRAB features (i.e., hypercalcemia, renal failure, anemia, and bone lesions) characteristic of MM, with only bone findings thought to be due to osteoporosis. She also developed a macrocytic anemia.

Treatment goals for SMM are to prevent or significantly delay the progression from SMM to MM. New treatment guidelines reflect advancements in management options for myelomas—particularly proteasome inhibitors (e.g., bortezomib) and immunomodulatory drugs (e.g., thalidomide, lenalidomide)—that provide additional therapeutic options, especially for those ineligible for hematopoietic cell therapy like our patient.[5] Identified risk factors for the progression from SMM to MM include: a bone marrow plasma greater than or equal to 10%, an increase in M-protein level greater or equal to 3 g/dL, and an abnormal free light chain (kappa/lambda) ratio (<0.125 or >8.0).[4,6] Our patient's M-protein at diagnosis was 2.7 g/dL and in response to treatment remained approximately 1 g/dL or lower. During her treatment course, our patient's kappa/lambda ratio remained abnormal at values around 0.10. However, large changes to her free light chain ratios or increases in her M-protein were not observed until her B-ALL diagnosis. Current risk factors did not predict our patient's aggressive transformation. She was started on treatment for standard-risk disease

and remained on immunomodulatory drugs for the majority of time leading up to her B-ALL diagnosis.

The sudden evolution from our patient's asymptomatic MM to B-ALL and her subsequent rapid decline was the most distinctive feature of this case. Supporting her diagnosis of B-ALL, our patient's karyotype analysis revealed interstitial deletions of 7q and 7p, both observed in B-ALL. Individuals with these deletions exhibit a loss of the gene coding for the tumor suppressor Ikaros family zinc finger 1 (IKZF1) and have similar features to Philadelphia chromosome-like B-ALL.[7] The prognosis of this gene mutation in adults is poor, with 5-year survival rates typically less than 25%.[8] Our patient's lymphoid progenitor cells exhibited instability early in her disease course. While therapy-related leukemia—specifically with alkylating agents and topoisomerase II inhibitors—has been previously documented,[9] there is no current evidence that proteasome inhibitors can induce tumorigenicity.

The progression of asymptomatic and symptomatic MM to B-ALL is not well documented. The underlying pathophysiology for this leukemic transformation—from a neoplastic proliferation of plasma cells to that of immature lymphocytes—could be due to a number of genetic mutations in addition to the deletion reported in our patient.[10] However, in our case, there are other unique branching evolutions from MM. AML has been reported in a patient with MM with concurrent myelodysplasia after similar treatment as our patient (e.g., bortezomib, thalidomide, dexamethasone).[11] Others described secondary plasma cell leukemia evolving from a MM patient after noting rouleaux formation of atypical cells with pale blue cytoplasm on peripheral blood smear. This patient was also treated with weekly bortezomib and dexamethasone which resulted in a decrease in the number of plasma cells in the peripheral blood, seemingly prolonging his survival.[12] Other investigators have highlighted the benefit of using karyotyping and fluorescent-in-situ hybridization (FISH) to assess the subsequent mutational patterns in patients with evolved MM.[13,14]

Until improved prediction of specific chromosomal changes—especially recurrent mutations—that result in clonal evolution of a hematologic malignancy, it is important to monitor for clonal evolutions in early MM. Prompt recognition via a variety of tests (e.g., genetic analysis, peripheral blood smear) may improve outcomes and help elucidate the behavior of aggressive hematologic neoplastic transformations as seen in our patient. Using FISH for molecular genetics analysis early in the course of SMM patients could be more sensitive in detecting genetic abnormalities that could induce hematologic evolution later in the disease course.[14] A better understanding of the mutational associations and branching patterns among hematologic malignancies is still needed to better target therapies for future patients.

REFERENCES

1. **Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR**. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003 Jan;78(1):21-33. PubMed PMID: 12528874.
2. **Siegel RL, Miller KD, Jemal A**. Cancer statistics, 2019. *CA Cancer J Clin*. 2019 Jan;69(1):7-34. doi: 10.3322/caac.21551. Epub 2019 Jan 8. PubMed PMID: 30620402.
3. **Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG, Miguel JF**. InternationalMyeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014 Nov;15(12):e538-48. doi: 10.1016/S1470-2045(14)70442-5. Epub 2014 Oct 26. Review. PubMed PMID: 25439696.
4. **Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, Larson DR, Plevak MF, Jelinek DF, Fonseca R, Melton LJ 3rd, Rajkumar SV**. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med*. 2007 Jun 21;356(25):2582-90. PubMed PMID: 17582068.
5. **Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Castillo J, Chandler JC, Costello C, Faiman M, Fung HC, Godby K, Hofmeister C, Holmberg L, Holstein S, Huff CA, Kang Y, Kassim A, Liedtke M, Malek E, Martin T, Neppalli VT, Omel J, Raje N, Singhal S, Somlo G, Stockerl-Goldstein K, Weber D, Yahalom J, Kumar R, Shead DA**. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018. *J Natl Compr Canc Netw*. 2018 Jan;16(1):11-20. doi: 10.6004/jnccn.2018.0002. PubMed PMID: 29295877.
6. **Larsen JT, Kumar SK, Dispenzieri A, Kyle RA, Katzmann JA, Rajkumar SV**. Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma. *Leukemia*. 2013 Apr;27(4):941-6. doi: 10.1038/leu.2012.296. Epub 2012 Oct 16. PubMed PMID: 23183428; PubMed Central PMCID: PMC3629951.
7. **Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, White D, Hughes TP, Le Beau MM, Pui CH, Relling MV, Shurtleff SA, Downing JR**. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature*. 2008 May 1;453(7191):110-4. doi: 10.1038/nature06866. Epub 2008 Apr 13. PubMed PMID:18408710.
8. **Jain N, Roberts KG, Jabbour E, Patel K, Eterovic AK, Chen K, Zweidler-McKay P, Lu X, Fawcett G, Wang SA, Konoplev S, Harvey RC, Chen IM, Payne-Turner D, Valentine M, Thomas D, Garcia-Manero G, Ravandi F, Cortes J, Kornblau S, O'Brien S, Pierce S, Jorgensen J, Shaw KR, Willman CL, Mullighan CG, Kantarjian**

H, Konopleva M. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood*. 2017 Feb 2;129(5):572-581. doi: 10.1182/blood-2016-07-726588. Epub 2016 Dec 5. PubMed PMID: 27919910; PubMed Central PMCID: PMC5290985.

9. **Pedersen-Bjergaard J**. Insights into leukemogenesis from therapy-related leukemia. *N Engl J Med*. 2005 Apr 14;352(15):1591-4. PubMed PMID: 15829541.
10. **Bolli N, Avet-Loiseau H, Wedge DC, Van Loo P, Alexandrov LB, Martincorena I, Dawson KJ, Iorio F, Nik-Zainal S, Bignell GR, Hinton JW, Li Y, Tubio JM, McLaren S, O' Meara S, Butler AP, Teague JW, Mudie L, Anderson E, Rashid N, Tai YT, Shammas MA, Sperling AS, Fulciniti M, Richardson PG, Parmigiani G, Magrangeas F, Minvielle S, Moreau P, Attal M, Facon T, Futreal PA, Anderson KC, Campbell PJ, Munshi NC**. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. *Nat Commun*. 2014;5:2997. doi: 10.1038/ncomms3997. PubMed PMID: 24429703; PubMed Central PMCID: PMC3905727.
11. **Gu ZH, Xie X, Mao JJ, Guo HF**. Rapid evolving into acute myeloid leukemia in a patient with multiple myeloma and concurrent myelodysplasia after VTD therapy. *Int J Clin Exp Med*. 2015 Jun 15;8(6):10105-8. eCollection 2015. PubMed PMID: 26309708; PubMed Central PMCID: PMC4538129.
12. **Agarwal P, Nayak P, Singh PA, Mishra BK**. Leukaemic Transformation of Multiple Myeloma in Post Chemo-therapy Remission Phase. *J Clin Diagn Res*. 2016 Apr;10(4):ED23-4. doi: 10.7860/JCDR/2016/17370.7696. Epub 2016 Apr 1. PubMed PMID: 27190822; PubMed Central PMCID: PMC4866120.
13. **Bergsagel PL, Kuehl WM**. Molecular pathogenesis and a consequent classification of multiple myeloma. *J Clin Oncol*. 2005 Sep 10;23(26):6333-8. Review. PubMed PMID: 16155016.
14. **Pratt G**. Molecular aspects of multiple myeloma. *Mol Pathol*. 2002 Oct;55(5):273-83. Review. PubMed PMID: 12354927; PubMed Central PMCID: PMC1187254.