Original Article

Dysmegakaryocytopoiesis and Maintaining Platelet Count in Patients with Plasma Cell Neoplasm

Yasmin Mair,* Yan Zheng,* Donghong Cai

Department of Pathology, Buffalo General Hospital, State University of New York at Buffalo, Buffalo, NY, USA.
**These authors contributed equally to this project.*

Abstract

Background: Dysmegakaryocytopoiesis in patients with the plasma cell neoplasm (PCN) is rarely discussed in the literature. The puzzling phenomenon, which PCN patients maintaining normal platelet count even when the marrow is mostly replaced by plasma cells, is hardly explored. **Aim:** This study was aimed to determine the frequency of dysmegakaryocytopoiesis in PCN and the relationships between bone marrow (BM) plasma cell percentage, plasma cell immunomarkers, the severity of dysmegakaryocytopoiesis, and peripheral blood platelet count in PCN. **Materials and Methods:** We randomly selected 16 cases of PCN, among which 4 were with monoclonal gammopathy of undetermined significance and 12 were with plasma cell myeloma. **Results:** Our study showed that: (1) Dysmegakaryocytopoiesis was present in all the selected cases of PCN and its severity was not correlated with the percentage of the plasma cells in BM; (2) almost all patients maintained normal platelet count even when BM was mostly replaced by plasma cells; (3) immunomarkers of the neoplastic plasma cells were not associated with dysmegakaryocytopoiesis or maintaining of platelet count. The possible mechanisms behind dysmegakaryocytopoiesis and maintaining of platelet count were also discussed. **Conclusion:** Despite the universal presence of dysmegakaryocytopoiesis in PCN, the platelet count is maintained at normal range.

Keywords: Dysmegakaryocytopoiesis, Peripheral blood platelet count, Plasma cell neoplasm

Address for correspondence: Dr. Donghong Cai, Department of Pathology, Buffalo General Hospital, 100 High Street, Buffalo, NY 14203, USA.
E-mail: dcai2@hotmail.com

Introduction

Plasma cell neoplasm (PCN) is characterized by monoclonal plasma cell proliferation, including plasma cell myeloma (PCM), monoclonal gammopathy of undetermined significance (MGUS), and plasmacytoma.[1] MGUS is a pre-malignant disorder, defined by the presence of < 3 g/dL serum monoclonal (M) protein, < 10% bone marrow (BM) plasma cells, and the absence of anemia, hypercalcemia, lytic bone lesions, or renal failure and other end-organ damages. In contrast, the diagnostic criteria for PCM include M protein > 3 g/dL and/or BM plasma cells > 10%, or whenever the presence of plasma cell-mediated end organ damages. The BM microenvironment plays an essential role in the pathogenesis of PCM. Stroma cells, extracellular matrix, and multiple secreted molecules in the BM have been shown to contribute to the proliferation, survival, and migration of the myeloma cells. In particular, interleukin 6 (IL-6) is a critical cytokine inducing the proliferation of myeloma cells.[2] Clinical studies have revealed that increased serum levels of IL-6 are associated with advanced tumor stages and poor survival rate in PCM patients.

Megakaryocytopoiesis occurs in the BM and is a multi-step process characterized by endomitotic DNA replication, cytoplasmatic expansion, proplatelet formation, and finally platelet release into the blood.[3] Defects in any of these steps can result in dysmegakaryocytopoiesis with abnormal megakaryocytes and low platelet counts. Multiple growth factors participate in megakaryocytopoiesis including thrombopoietin (TPO), granulocyte-macrophage colony-stimulating factor, IL-3, IL-6, IL-11, stem cell factor, FMS-like tyrosine kinase (FLT) ligand, fibroblast

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.112474

growth factor, erythropoietin, etc., TPO is the primary growth factor regulating megakaryocytic proliferation and differentiation and it functions to increase the number, size, and ploidy of megakaryocytes, as well as proplatelet formation and platelet release.[4] Cytokine IL-6 indirectly promotes megakaryocytopoiesis by up-regulating TPO production, particular in the context of inflammation.[5] Normal megakaryocytes have a single mutilobated nucleus. The morphological abnormalities of dysplastic megakaryocytes include micromegakaryocyte, mononuclear megakaryocyte that lacks normal nuclear lobation (hypolobation), and hyperlobated megakaryocyte with multiple small separated nuclei (mutinucleation).[6] Dysmegakaryocytopoiesis is one of the hallmarks of myelodysplastic syndrome (MDS), a collection of disorders featuring impaired hematopoiesis of one or multiple major cell lineages.[7] Besides MDS, dysplastic megakaryocytes have also been observed in acute myeloid leukemia (AML) and idiopathic thrombocytopenic purpura.[8,9] Of note, the presence of dysplastic megakaryocytes is associated with a poor response to chemotherapy in AML patients.

Dysmegakaryocytopoiesis has been rarely reported in PCN based on our literature search, and the maintaining of peripheral platelet count at a normal level, even in advanced PCM, has barely been discussed. In the current report, we studied the relationship between peripheral blood platelet count, BM dysmegakaryocytopoiesis and PCN in 16 patients. Our data showed that the dysmegakaryocytopoiesis is frequently observed in patients with PCN, yet the platelet count is maintained at normal range even when the BM is largely replaced by neoplastic plasma cells. The possible mechanism behind this phenomenon, the interplay between IL-6 and TPO was also discussed.

Materials and Methods

Case selection

Sixteen patients with PCN were randomly selected from the archived cases in the Department of Pathology, Buffalo General Hospital, Buffalo, NY. All of these cases were diagnosed as MGUS or PCM prior to treatment during 2010-2012. All 16 cases had adequate BM biopsy and aspirate smear slides and good quality of immunostaining including CD138, kappa, lambda, CD56 and cyclinD1. Patients' history, radiology findings, complete blood count, data of serum protein electrophoresis and immunofixation electrophoresis were extracted from their electronic records. Patients were de-identified and listed as case 1 to case 16. The results of this study are purely for research purpose and will not be used as quality assurance or patient care in any circumstances.

This study belongs to the category of "Review of Medical Records" in the guidelines of Institutional Review Board (IRB) of State University of New York at Buffalo, Buffalo, NY, and therefore, is not considered human subject research and does not require IRB review and approval (www.research.buffalo.edu/rsp/irb/hsirb/guidelines/case_reporting.cfm).

Case review

Every case was independently reviewed by three pathologists. For assessing dysmegakaryocytopoiesis, morphologic manifestations of dysplasia described in the chapter of MDSs/Neoplasms of WHO Classification (2008)[6] were adopted as our criteria. Specifically, dysmegakaryocytopoiesis includes three morphologic variants: Micromegakaryocytes, nuclear hypolobation, and multinucleation. Special attention was given to separate immature megakaryocytes and anaplastic plasma cells from real dysplastic megakaryocytes. Immature megakaryocytes were defined as young form of megakaryocytes with scant bluish vacuolated cytoplasm and non-lobulated nucleus which showed immature chromatin and occupied most of the cell.[10] Megakaryocyte-like giant plasma cells were excluded by CD138 immunostain.[11] Minimally 30 megakaryocytes per case were counted and the percentage of dysplasia was classified as follows: < 10%, mild dysplasia; 10-50%, moderate dysplasia; > 50%, severe dysplasia. All the results are listed in Table 1.

Results

As shown in Table 1, percentage of neoplastic plasma cells in BM ranged from 3% to 85%. According to the WHO classification (2008),[6] 4 patients were diagnosed as MGUS and 12 of them were diagnosed with PCM. Platelet counts ranged from 113 to 433 K/μL with an average of 267 K/μL. Of note, only one patient had slightly decreased platelet count (113 K/μL), all other patients maintained platelet count at a normal level. Regarding the severity of dysmegakaryocytopoiesis, our observation revealed 2 cases with mild, 5 with moderate, and 9 with severe dysplasia. As shown in Table 1, the grade of dysplasia was not correlated with the amount of plasma cells in BM: Two patients in the mild category showed 25% and 50% plasma cells in BM while in the severe category, patients had as low as 3% plasma cells in the marrow. Analysis on expression of CD56, cyclinD1, cytoplasmic kappa, and cytoplasmic lambda revealed no correlation of these antigen markers with the severity of dysmegakaryocytopoiesis.

Discussion

In the present study, we characterized in detail the peripheral blood platelet count and dysmegakaryocytopoiesis in 16

Table 1: Patient information and related CBC, plasma cell percentage, antigen markers, and grading of dysmegakaryocytopoiesis

Case	Gender	Age (years)	CBC			CD138+	CD56	D1	κ	Λ	Dysmegakaryocytopoiesis		
			WBC (K/μL)	HGB (g/dL)	PLT (K/μL)	% plasma cell					Mild	Moderate	Severe
1	Female	55	2.6	10.5	178	60	(+)	(+)	(+)	(−)			(+)
2	Female	83	5	12	222	75	(−)	(−)	(+)	(−)			(+)
3	Female	71	N/A	N/A	N/A	30	(+)	(+)	(−)	(+)			(+)
4	Male	68	6.22	9.7	433	50	(+)	(+)	N/A	N/A			(+)
5	Male	71	3.5	8	223	85	(+)	(−)	(+)	(−)			(+)
6	Female	66	5.47	11.9	212	40	(+)	(−)	(+)	(−)		(+)	
7	Male	73	8.46	13.3	411	50	(+)	(+)	(+)	(−)			(+)
8	Male	83	7.8	9.87	294	50	(−)	(+)	(-)	(+)	(+)		
9	Female	79	10.7	12	288	70	(+)	(−)	N/A	N/A			(+)
10	Male	56	7.36	14	289	3	(+)	(−)	(+)	(+)			(+)
11	Female	83	11.01	10.7	494	70	(−)	(−)	(−)	(−)		(+)	
12	Male	77	6.8	14.01	199	8	(−)	(−)	(+)	(−)		(+)	
13	Male	82	4.9	12.3	113	25	(−)	(+)	(−)	(+)	(+)		
14	Male	54	7.5	15.1	284	5	(+)	(−)	(−)	(+)		(+)	
15	Male	46	5.8	15.9	234	5	(−)	(−)	(−)	(+)			(+)
16	Male	82	N/A	N/A	N/A	12	(+)	(−)	(−)	(+)		(+)	

Dysmegakaryocytopoiesis was graded as mild: <10%, Moderate: 10-50%, Severe: >50%, D1: CyclinD1, κ: Kappa light chain, Λ: Lambda light chain, CBC: Complete blood count, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet

randomly selected patients with PCN (MGUS and PCM). We demonstrated that dysplasia of megakaryocytes in PCN was universal, with over half of the patients showing more than 50% of their megakaryocytes dysplastic. Furthermore, almost all patients maintained peripheral blood platelet count at a normal level even when some of their BMs were almost completely replaced by neoplastic plasma cells.

Dysmegakaryocytopoiesis can be seen in many benign or malignant medical situations, such as idiopathic thrombocytopenia purpura, infection-associated thrombocytopenia, megaloblastic anemia, MDS, acute lymphoblastic leukemia, and AML.[7-9,12] The mechanism behind this phenomenon is not completely understood. Some studies have shown that interactions between megakaryocytes and their environment, mediated by various cytokines and growth factors, are pivotal for the formation of dysplastic megakaryocytes. Singer *et al*. found that dysmegakaryocytopoiesis was proportional to the levels of IL-6 and IL-18 while inversely correlated with levels of TNF-alpha and CRP in BM.[13] Other studies showed that PCN patients had higher levels of TPO and IL-6 than healthy controls[14] and TNF-alpha was one of the key factors in plasma cell differentiation, proliferation and survival.[15,16] Therefore, it is not a surprise to detect dysmegakaryocytopoiesis in patient with PCN, although surprisingly, this phenomenon had rarely been mentioned in literature. In our study, we found that dysmegakaryocytopoiesis was universal, presented in all of our randomly selected cases, and was not correlated with the amount of plasma cells in BM.

Another interesting finding in our study was that almost all of the patients maintained normal level of their platelet count in peripheral blood, even with the fact that some of the patients' BM had been largely replaced by neoplastic plasma cells. IL-6, the most potent factor in the pathogenesis of PCM has been shown to increase TPO levels by up-regulating its hepatic production.[5] Studies also showed that PCN patients had higher levels of TPO and IL-6 than healthy controls.[14] Considering the essential role of TPO in thrombocytopoiesis, the platelet counts might be well-preserved by an increase in megakaryopoiesis and thrombocytopoiesis, despite the presence of dysmegakaryocytopoiesis and reduction of normal marrow elements by expansion of plasma cells.

Dysplastic megakaryocytes have been traditionally seen as a feature of MDS, which is characterized by cytopenia (s) and/or dysplasia in one or more of the major cell lineages with an increased risk of development of AML.[7] Dysplastic megakaryocytes in PCN, particularly in those patients with the MGUS (<10% BM plasma cells), add confusion to differentiate MDS from MGUS. In our series, 4 patients had only 3-8% BM plasma cells, which were easily ignored on H and E sections and were only highlighted by CD138 immunostain, yet the dysplasia of megakaryocytes was prominent both on tissue sections and aspirate smear [Figure 1a and b as an example case]. Therefore, extra caution should be exercised in analyzing BM elements, and PCN should always be in the differential list.

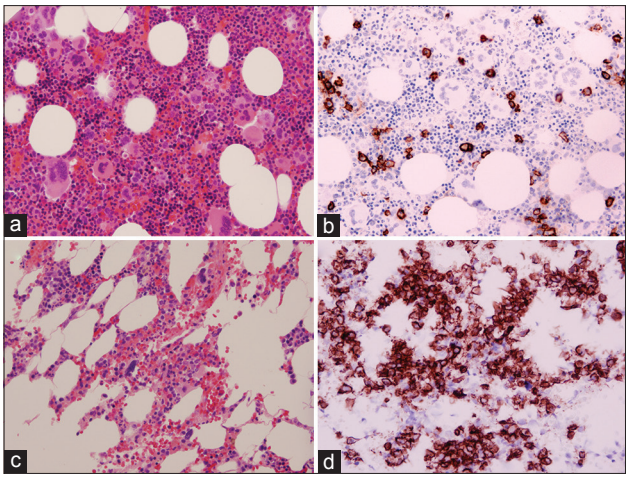

Figure 1: Two representative cases of plasma cell neoplasm. (a and b) Bone marrow H and E section (a) and CD138 immunostain (b) for plasma cells in one patient. Many dysplastic megakaryocytes are shown, yet the plasma cells are only about 3% of marrow cells. This patient was diagnosed as monoclonal gammopathy of undetermined significance. (c and d) Bone marrow H and E section (c) and CD138 immunostain (d) for plasma cells in another patient. Dysplastic megakaryocytes are readily seen, and marrow plasma cells are very high. This patient was diagnosed as plasma cell myeloma

Conclusion

In conclusion, the abnormalities found in PCN are not confined to the plasma cell compartment. The identification of dysplastic megakaryocytes and the ability of patients to maintain platelet count at a normal level are very interesting in the processes of both pathologic diagnosis and clinical patient care. More basic research is needed to clarify the mechanisms behind these findings.

References

1. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. Lancet 2009;374:324-39.
2. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nat Rev Cancer 2007;7:585-98.
3. Deutsch VR, Tomer A. Megakaryocyte development and platelet production. Br J Haematol 2006;134:453-66.
4. Geddis AE. Megakaryopoiesis. Semin Hematol 2010;47:212-9.
5. Kaser A, Brandacher G, Steurer W, Kaser S, Offner FA, Zoller H, *et al*. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: Role in inflammatory thrombocytosis. Blood 2001;98:2720-5.
6. IARC. WHO classification of tumours of haematopoietic and lymphoid tissue (IARC WHO classification of tumours). 4th ed. World Health Organization; 2008.
7. Foran JM, Shammo JM. Clinical presentation, diagnosis, and prognosis of myelodysplastic syndromes. Am J Med 2012;125:S6-13.
8. Jinnai I, Tomonaga M, Kuriyama K, Matsuo T, Nonaka H, Amenomori T, *et al*. Dysmegakaryocytopoiesis in acute leukaemias: Its predominance in myelomonocytic (M4) leukaemia and implication for poor response to chemotherapy. Br J Haematol 1987;66:467-72.
9. Wang L, Li Y, Hou M. Idiopathic thrombocytopenic purpura and dysmegakaryocytopoiesis. Crit Rev Oncol Hematol 2007;64:83-9.
10. McKenzie SB. Textbook of Hematology. 2nd ed. Williams and Wilkins; 1996.
11. Wang C, Amato D. Megakaryocyte-like giant myeloma cells. Am J Hematol 2004;77:311-2.
12. Muhury M, Mathai AM, Rai S, Naik R, Pai MR, Sinha R. Megakaryocytic alterations in thrombocytopenia: A bone marrow aspiration study. Indian J Pathol Microbiol 2009;52:490-4.
13. Singer MK, Assem M, Abdel Ghaffar AB, Morcos NY. Cytokine profiling as a prognostic markers in chronic myeloid leukemia patients. Egypt J Immunol 2011;18:37-46.
14. Ozkurt ZN, Yağci M, Sucak GT, Kirazli S, Haznedar R. Thrombopoietic cytokines and platelet count in multiple myeloma. Platelets 2010;21:33-6.
15. Jourdan M, Tarte K, Legouffe E, Brochier J, Rossi JF, Klein B. Tumor necrosis factor is a survival and proliferation factor for human myeloma cells. Eur Cytokine Netw 1999;10:65-70.
16. Di Girolamo N, Visvanathan K, Lloyd A, Wakefield D. Expression of TNF-alpha by human plasma cells in chronic inflammation. J Leukoc Biol 1997;61:667-78.

How to cite this article: Mair Y, Zheng Y, Cai D. Dysmegakaryocytopoiesis and maintaining platelet count in patients with plasma cell neoplasm. North Am J Med Sci 2013;5:316-9.

Source of Support: Nil. **Conflict of Interest:** None declared.