

Original Article

Concomitant *de novo* myeloid and plasma cell disorders are frequently associated with low-risk cytogenetic abnormalities: a single institutional clinicopathologic study of 32 cases

Haipeng Shao¹, Taiga Nishihori³, Rachid Baz², Melissa Alsina³, Alan F List², Rami S Komrokji², Kenneth H Shain², Ling Zhang¹

Departments of ¹Hematopathology and Laboratory Medicine, ²Malignant Hematology, ³Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

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Abstract: We retrospectively reviewed 32 patients (median age 71.5 years) with concomitant *de novo* myeloid and plasma cell disorders (PCD) treated at our center between 2005 and 2015. None of the patients had received prior cytotoxic chemotherapy or radiotherapy before diagnosis. Myeloid neoplasms included 20 myelodysplastic syndromes (MDS; 63%), 7 acute myeloid leukemias (AML; 22%), 4 myelodysplastic and myeloproliferative neoplasms (12.5%), and 1 primary myelofibrosis (3%). A minority of patients harbored complex karyotype (7%) or other cytogenetic abnormalities (28%). Fifteen MDS patients were categorized as low/intermediate-1 risk according to the International Prognostic Scoring System. Transformation rate from MDS to AML was 35%, similar to previous reports. All patients had subclinical/asymptomatic PCD. FISH myeloma studies identified 8 patients (27%) with unfavorable risk cytogenetic abnormalities at diagnosis, but none progressed to symptomatic myeloma. Thus, the study showed frequent concurrence of low-risk MDS and subclinical PCD with a natural history similar to *de novo* MDS.

Keywords: Myelodysplastic syndromes, acute myeloid leukemia, multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), cytogenetics

Introduction

Plasma cell disorders (PCD) are derived from terminally differentiated, immunoglobulin-secreting post-germinal center B cells. The spectrum of PCD mainly includes monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and symptomatic myeloma or multiple myeloma. MGUS is characterized by the presence of a small serum monoclonal protein (≤ 3 g/dL), $<10\%$ bone marrow plasma cells, no lytic bone lesion and absence of end-organ damage, whereas SMM is characterized by a larger serum monoclonal protein (≥ 3 g/dL) or urine monoclonal protein (≥ 500 mg per 24 hours) and clonal bone marrow plasmacytosis (10% to 60%) and lacks multiple myeloma-defining events or amyloidosis [1]. Both MGUS and SMM represent an early phase of PCD and are con-

sidered to be asymptomatic or subclinical with a very indolent clinical course. On the other hand, symptomatic myeloma or multiple myeloma is mainly distinguished from the other 2 subclinical PCDs by the presence of clonal plasma cells $>10\%$ of bone marrow cellularity or biopsy-proven plasmacytoma and evidence of end-organ or tissue damage (hypercalcemia, renal failure, anemia, and bone disease, or $>60\%$ of bone marrow plasma cell infiltration) [1].

MGUS is the most common subtype of plasma cell dyscrasia, occurring in 3% to 4% of individuals over 50 years of age and 5.3% of individuals over 70 years of age [2-4]. It is considered a noncancerous or precursor condition with a risk of progression to lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia or overt PCD (SMM or multiple myeloma) of approximately 0.5% to 1% per year [2, 5-8]. SMM is an

intermediate phase between MGUS and symptomatic multiple myeloma and demonstrates heterogeneous clinical features toward either an indolent or aggressive course. Approximately 10% of patients with SMM may progress to symptomatic multiple myeloma the first 5 years after diagnosis, which then decreases to 3% per year for the next 5 years and 1.5% per year thereafter upon cytogenetic risks [9, 10]. The treatment of MGUS includes only a clinical and biological surveillance according to international guidelines available for MGUS diagnosis and follow-up [1]. Although monitoring is usually recommended for MGUS and SMM, symptomatic multiple myeloma is treated with long-term systemic therapy [1]. The decision to initiate myeloma therapy is related to the identification of related CRAB criteria (Calcium elevation in the blood; Renal insufficiency; Anemia; and lytic Bone lesions or osteoporosis); an underlying myeloid disorder may obscure the clinical presentation or result in inappropriate therapy. For patients with multiple myeloma, current therapy involves induction therapy with novel agent-based combination regimens, high-dose melphalan followed by autologous stem cell support, and maintenance therapy [11]. Despite these contemporary therapeutic strategies and the presence of next-generation proteasome inhibitors, immunomodulating agents and histone deacetylase inhibitors continue to improve progression-free survival and overall survival [12-14].

Secondary myeloid neoplasms, particularly myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), have been occasionally reported in patients with PCD [15, 16], which is often attributed to use of prior alkylating agents (that is, melphalan and/or cyclophosphamide presumably resulting in DNA damage) [17]. Recent studies have shown increased risk of development of MDS/AML with the use of maintenance lenalidomide in the context of melphalan exposure [14, 18-20]. Interestingly, recent studies have also shown increased risk of development of MDS/AML not only in patients with malignant PCD but also in patients with MGUS without intervening therapy [21, 22]. These findings suggest that some factors beyond chemotherapy might be involved in myeloid neoplasm development in patients with PCD. The development of concomitant *de novo* myeloid disorder and PCD

remains rare but is observed. To date, a detailed clinicopathologic analysis of such cases is limited. In this study, we report the clinicopathologic features of 32 patients with concomitant *de novo* myeloid disorders and PCD unrelated to chemotherapy or radiotherapy. Cytogenetic findings and clinical outcomes are both presented.

Materials and methods

Case selection

The study was approved by the institutional review board of the University of South Florida. Thirty-two patients who had untreated SMM or MGUS with concomitant *de novo* MDS, AML, myeloproliferative or myelodysplastic/myeloproliferative neoplasms were identified from our institutional pathology database between January 2005 and August 2015. The diagnoses of plasma cell and myeloid neoplasms were rendered according to the 2008 World Health Organization (WHO) classification [23]. Clinical information and follow-up were obtained from patients' medical records. Relevant clinical information is summarized in **Table 1**.

Conventional cytogenetic analyses

Cytogenetic analyses were routinely performed with use of anticoagulated bone marrow aspirates. Chromosomes in metaphase were G banded on both mitogen-stimulated and unstimulated bone marrow cells using standard cytogenetic techniques after 24-hour culture. G-banded karyotypes were prepared, and representatives of any clones were detected. Karyotypes were classified according to the International System for Human Cytogenetic Nomenclature recommendations [24].

Fluorescence in situ hybridization

For fluorescence in situ hybridization (FISH) analyses of MDS, bone marrow specimens were subjected to hypotonic treatment with 0.075 M sodium chloride and then fixed with fixative (methanol and acidic acid at 3:1 vol/vol). Cell suspension was added to slides and treated with 0.005% (wt/vol) pepsin solution for 10 minutes, followed by dehydration with 70%, 85%, and 100% ethanol for 2 minutes each. Hybridization was performed in five slides with 10 μ L of each of 5 probe sets: 5q31/5p15.31, 7q22.1/7q31, 17p13/17cen, 20q12/

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Table 1. Clinical information of 32 patients with concomitant plasma cell disorder and *de novo* myeloid neoplasm

Case	Age (yr*)/ Sex	Plasma cell neoplasm		Myeloid neoplasm		MDS IPSS at initial DX	Therapy for myeloid neoplasm and progressed disease	Therapy for plasma cell neoplasm	Follow-up, (mo)	Outcome
		Initial Dx	Disease progress	Initial Dx	Disease progress					
1	75/M	SMM	No	RCMD	No	Int-1/0.5	Azacitidine	No	34	Dead*
2	59/F	MGUS	No	Isolated del(5q)	No	Int-1/0.5	Lenalidomide/Azacitidine	No	64	Dead*
3	67/M	MGUS	No	RARS-T	CMML AML	Low/0	Anagrelide, hydroxyurea, epoetin alfa/azacitidine	No	53	Dead
4	72/M	SMM	No	RCMD	RAEB-2 AML	Int-1/0.5	Azacitidine/Lenalidomide/ Onconova 1910/Melphalan	No	95	Dead
5	70/F	MGUS	sPCM	RARS	No	Low/0	Lenalidomide/dexamethasone	No	14	Alive
6	74/M	SMM	No	RAEB-2	AML	Int-2/1.5	Lenalidomide, azacitidine	No	52	Dead
7	64/M	MGUS	sPCM	RAEB-1	AML	Int-1/0.5	Azacitidine/CLAG-M	No	28	Dead
8	71/F	SMM	No	CMML-1	CMML-2	NA	Azacitidine	Lenalidomide, bortezomib	70	Alive
9	71/M	MGUS	sPCM	RCMD-RS	No	Low/0	Azacitidine	No	52	Alive
10	71/M	MGUS	sPCM	RCMD	No	Int-1/0.5	Epoetin alfa, G-CSF	No	20	Alive
11	74/M	SMM	No	AML	NA	NA	Azacitidine	No	2	Alive
12	57/M	SMM	No	RCMD	AML	Int-1/0.5	Azacitidine	No	7	Alive
13	59/M	SMM	No	AML	NA	NA	7+3/CLAG-M/Azacitidine	No	15	Dead
14	74/M	MGUS	No	RCMD-RS	No	Low/0	No	No	10	Dead*
15	71/M	SMM	No	RAEB-2	AML	High/2.5	Azacitidine	No	13	Dead
16	67/M	MGUS	No	RARS	No	Int-1/0.5	Lenalidomide	No	9	Alive
17	80/M	MGUS	No	AML with inv (16)	NA	NA	7+3	No	28	Dead
18	72/F	MGUS	No	CMML-1	CMML-2	NA	Azacitidine/CLAG-M	No	22	Alive
19	79/M	MGUS	No	RCMD	No	Int-1/0.5	Azacitidine, G-CSF	No	24	Alive
20	64/F	SMM	NA	RAEB-2	No	Int-2/1.5	Azacitidine, lenalidomide/MUD Allo-HSCT	No	20	Alive
21	74/M	SMM	No	RCMD	RAEB-1	Int-1/1	Azacitidine	No	12	Alive
22	74/M	SMM	NA	AML	NA	NA	7+3	Bortezomib, dexamethasone	8	Alive
23	74/F	SMM	No	AML	NA	NA	Unknown	Unknown	5	Lost f/u
24	64/F	MGUS	No	RCMD	RAEB-2	Low/0	Azacitidine cytarabine, daunorubicin	No	38	Alive
25	76/M	MGUS	No	RCMD	RAEB-2 AML	Int-2/1.5	Azacitidine	No	70	Alive

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26	59/M	SMM	NA	AML	NA	NA	Azacitidine, lenalidomide allo-HSCT	No	8	Alive
27	57/M	SMM	No	CMML-1	No	NA	Filgrastim, epoetin alfa	Bortezomib dexamethasone lenalidomide	143	Alive
28	74/M	MGUS	No	RCMD	No	Low/0	Azacitidine, lenalidomide, cenersen	No	56	Alive
29	80/M	SMM	No	RAEB-2	AML	Int-2/2	Azacitidine/Lenalidomide	Low dose melphalan and prednisone	17	Alive
30	81/M	MGUS	No	AML	NA	NA	Azacitidine	No	8	Alive
31	75/M	SMM	No	RCMD	No	Int-1/1	Procrit	No	19	Alive
32	71/F	SMM	No	PMF	No	NA	No	Bortezomib dexamethasone	11	Alive

M, Male; F, Female; Dx, Diagnosis; Yr, Years; NA, Not applicable; MDS, Myelodysplastic syndromes; IPSS, International Prognostic Scoring System; Int-1, Intermediate risk-1; Int-2, Intermediate risk-2; MGUS, Monoclonal gammopathy of undetermined significance; Mo: Months, PCM, Plasma cell myeloma; SMM, Smoldering plasma cell myeloma; RAEB-1, Refractory anemia with excess blasts, type 1; RAEB-2, Refractory anemia with excess blasts, type 2; RARS, Refractory anemia with ring sideroblasts; RARS-T, Refractory anemia with ring sideroblasts associated with marked thrombocytosis; RCMD, Refractory cytopenia with multilineage dysplasia; RCMD-RS, Refractory cytopenia with multilineage dysplasia and ringed sideroblasts; AML, Acute myeloid leukemia; CMML, Chronic myelomonocytic leukemia; 7+3, Cytarabine (7 days) and an anthracycline (daunorubicin, 3 days); CLAG-M, Cladribine, Cytarabine, Mitoxantrone, granulocyte colony stimulating factor; G-CSF, Granulocyte colony stimulating factor; MUD allo-HSCT, Matched unrelated donor allogeneic hematopoietic stem cell transplantation. *Patient died of concurrent lung cancer.

q13.12, and D8Z2 (Cytocell). Specimens were coverslipped, and slides were sealed with rubber cement. The specimens were subjected to denaturation at 75°C for 3 minutes and hybridized at 37°C for 16 hours. The slides were washed in 0.4 × saline-sodium citrate at pH 7.2 and then counterstained with 4'6-diamidino-2-phenylindole. Results were analyzed on a Leica DM 5500B fluorescent microscope. For each probe test, at least 200 cells were examined.

For FISH analysis of PCD, plasma cells from bone marrow aspirates were enriched through a cell sorting procedure using magnetic beads coated with anti CD138 antibody (Integrated Oncology/Labcorp, Inc.). The enriched cell populations were then analyzed with the use of a standard multiple myeloma FISH assay. The standard assay targeted the *IGH* gene for fusions with *FGFR3*, *CCND1*, and *MAF*. Additional targets were 1q21(*CKS1B*), 13q14(*LEU1*), and 17p13(*TP53*). FISH hybridizations were carried out using standard techniques with 200 interphase cells counted for each target.

Results

Clinical features

The clinical features of the 32 patients are summarized in **Tables 1** and **2**. Twenty-four patients were male (75%) and 8 were female (25%). The median age was 71.5 (range from 57 to 81 years) at diagnosis. Of the 32 patients, 26 patients (81%) had myeloid neoplasm and PCD diagnosed simultaneously on the same bone marrow biopsy. Four patients (13%; patients 5, 9, 15, and 17) had a history of MGUS (ranging from 6 months to 20 years) and received no cytotoxic treatment before development of myeloid neoplasm. Two patients (6%; patients 4 and 28) had a diagnosis of MDS subcategorized as refractory cytopenia with multilineage dysplasia (RCMD), 7 and 3 years, respectively, before the development of PCD (**Table 1**). None of the two patients received prior cytotoxic chemotherapy or immunomodulatory therapy for their MDS. Patients with PCD were divided into 2 groups; 15 patients (47%) with MGUS, and the rest (53%) with SMM. Of the 26 patients with available serum protein electrophoresis and immunofixation data, 14 displayed IgG (54%), 9 with IgA (34%), 1 with IgM (4%), and 2 with serum-free light chain only

(8%). Serum M-spike values at time of diagnosis ranged from 0.2 to 1.8 g/dL (median 1.2 g/dL). Clonality was detected in 30 patients according to serum-free light chain test, including clonal kappa light chain in 21 patients (70%) and clonal lambda light chain in 9 patients (30%). Four patients (13%; patients 5, 7, 9, and 10) with MGUS showed progression to SMM based on increased plasma cells in subsequent bone marrow biopsies and overtly increased serum immunoglobulin levels. However, none of the patients developed myeloma-related organ or tissue damage to be qualified as MM.

The diagnosed myeloid neoplasms included MDS in 20 cases (63%), AML in 7 cases (22%), myelodysplastic/myeloproliferative neoplasms in 4 cases including 3 chronic myelomonocytic leukemia, type 1 (CMML-1) (9%), 1 refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) (3%), and 1 myeloproliferative neoplasm/primary myelofibrosis (3%). At time of diagnosis of myeloid neoplasms, complete blood counts were available for 31 patients, with pancytopenia in 13 patients (42%), bicytopenia in 8 (25%), and borderline cytopenia or unicytopenia in 10 patients (32%) (**Table 1**). Of the 20 patients with MDS, 15 patients (75%) were categorized as low/intermediate-1 risk and 5 patients (25%) were intermediate-2 or high risk according to the International Prognostic Scoring System (IPSS).

Twelve patients (38%) with myeloid neoplasm demonstrated progression of myeloid disease. Two patients (patients 21 and 24) with RCMD had progression to refractory anemia with excess blasts (RAEB), whereas 7 patients with various subtypes of MDS (patients 4, 6, 7, 12, 15, 25, and 29) had progression to AML. The patient with RARS-T (patient 2) showed sequential progression of disease to CMML and AML. Two of the three patients with CMML-1 (patients 8 and 18) showed progression of disease to CMML-2 but without further progression to AML.

In regard to therapy of concomitant neoplasms, the majority of patients with MGUS or SMM remained on observation. Of note, only 5 SMM patients (16%; patients 8, 22, 27, 29, and 32) received therapy for their PCD with immunomodulatory agents (bortezomib or lenalidomide) or low-dose melphalan plus steroids and

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Table 2. Laboratory findings of 32 patients with concomitant plasma cell disorder and *de novo* myeloid neoplasm

Case No.	CBC (WBC/Hb/ Plt)	M spike (g/L)	Bone Marrow Examination							FISH for MDS	FISH for PCM
			Blasts (%)	PC (%)	Ig HC	Ig LC	Cytogenetics*				
1	2.5/8.7/98	1.5	0	15	IgG	k	46,XY[20]		ND	ND	
2	2.2/9.9/124	0.3	4	7.5	IgA	l	46,XX,del(5)(q13q33)[9]/46,XX[6]		-5q	Normal	
3	5.1/9.5/600	ND	3	9	ND	ND	46,XY[20] (RARS-T)		ND	ND	
			3	5			46,XY,del(7)(p11.2p21)[5]/46,XY[15] (MDS/MPN, Unclassifiable)		ND		
			4	2			46,XY,del(7)(p11.2p21)[1]/46,XY,add(2)(q36)[cp4]/46,XY[19] (CMML)		ND		
			32	2			46,XY,der(15)t(1;15)(q21;p11.2)[7]/46,XY[13] (AML)		Normal		
4	1.1/9.4/81	ND	3	13	IgG	k	46,XY[20] (RCMD)		Normal	ND	
			12	15			46,XY[20] (RAEB-2)		-7q		
			21	16			45,XY,-7[18]/46,XY[2] (AML)		-7q		
5	4.7/9/113	1	1	8	IgG	k	46,XX[20]		Normal	Normal	
6	3.1/14.5/252	ND	10	20	IgA	k	46,XY[20] (RAEB-2)		Normal	ND	
			21	15			46,XY[20] (AML)		Normal		
7	4.6/13.8/107	0.3	8	6	IgA	l	45,XY,del(20)(q11.2),-22[3]/46,XY[4] (RAEB-1)		-20q	CCND1/IGH t(11;14)	
			40	20			46,XY,del(20)(q11.2)[16]/46,XY[4] (AML)		-20q		
8	13.5/12/208	1.5	1.5	10	IgA	k	46,XX[20] (CMML-1)		Normal	IGH/FGFR3 t(4:14) 3 and 4 copies	
			10	16			46,XX[20] (CMML-2)			1q21 Monosomy 13	
9	4.4/10.9/206	1.1	0.5	5	IgG	k	45,X,-Y[7]/46,XY[13]		Normal	4 or >4 copies of 1q21, trisomy and tetrasomy 17	
10	1.2/11/114	0.9	2.2	7	IgG	l	46,XY[20]		Normal	ND	
11	2.3/10.2/67	1.6	23	22	IgG	k	46,XY[20]		Normal	CCND1/IGH t(11;14), monosomy 13	
12	1.1/6.1/16	1.5	0.5	17	IgG	k	Not available (RCMD)		-20q	ND	
			25	17			46,XY,del(16)(q23.2),del(20)(q11.2)[20] (AML)		-20q		
13	4.4/9.4/92	0.6	70	15	IgG	k	46,XY, add(7)(q34)[20] (original AML)		Normal	Normal	
							46,XY,add(1)(p36.3),add(5)(q15),?add(17)(p11.2),del(18)(q21)[cp13]/46,XY[7](relapsed AML)		-5q		
14	6.2/7.4/188	0.3	3	7	IgA	l	46,XY[20]		Normal	ND	
15	2.6/11.4/189	1.8	15	18	NA	k	46,XY, add(1)(q42), add(2)(q33),-5, add(12)(p13), del(14)(q31q33), der(19)t(3;19)(q25;p13.3) +21, +22[6]/46,XY[14] (RAEB-2)		-5q	ND	
			25	18			46,XY,add(1)(q32),del(2)(q32q33),-3,-5,add(12)(p12),add(19)(p13.3),+21,+22[cp12]/46,XY[8] (AML)		-5q		
16	2.7/7.9/282	ND	1.5	8	IgG	k	46,XY[20]		Normal	Normal	
17	0.3/8.3/12	1.1	40	8	IgG	l	46,XY,inv(16)(p13q22)		NA	Normal	
18	39.2/10/144	ND	1.2	4	IgA	k	46,XX[20] (CMML-1)		Normal	ND	
			15	2			46,XX[20] (CMML-2)				
19	3.3/8.2/55	ND	2	5	IgG	l	46,XY,del(20)(q11.2)[6]/46,XY[14]		ND	ND	
20	7.4/7.8/125	1.3	18	18	IgA	k	46,XX[20]		Normal	3 and 4 copies of 1q21, trisomy 17	

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21	5.4/9.6/209	0.2	1.8	8	No	I	ND		ND	CCND1/IGH
			5	10			47,XY,+8[14]/46,XY[6] (RAEB-1)			
22	42.4/8.5/996/ (29% blasts)	No	32	60	ND	k	45,X,-Y[3]/46,XY[12]	Normal	ND	
23	31.7/9.5/69/ (28% blasts)	ND	86	15	ND	k	ND	ND	ND	
24	4.6/5.6/163	ND	2	4	ND	k	46,XY,i(17)(q10)[3]/46,XY[17]	-17p	ND	
25	2.4/9/72	ND	2.5	1	ND	ND	47,XY,+8[15]/47, idem,del5(q22q35)[2]/46,XY,t(3;5)(q25;q13)[3] (RCMD)	ND	ND	
							47,XY,+8[4]/46,XY[16] (RAEB-2)	ND		
							47,XY,+8[17]/46,XY,t(3;5)(q26;q15)[1]/46,XY[2] (AML)	+8		
26	1.1/8.2/83	1	20	18	IgA	I	43-45,XY,add(3)(p21),-5,-7,+8,dic(17;20)(p11.2q11.2),+mar[cp20]	-5q, -7q, +8, -17p, -20q	ND	
27	3.7/12/106	1.3	2	20	IgG	k	47,XY,+8[2]/46,XY[18]	+8	CCND1/IGH -13q	
28	NA	1.6	2	5-9	IgM	k	46,XY[20]	Normal	ND	
29	2.5/9.2/339	No	15	24.8	No	k	46,XY[20] (RAEB-2) 47,XY,del(7)(q22),+14[cp16] (AML)	-7	+1p, +1q, -13q, +14q, -17p	
30	2.2/11.5/88	ND	23	5	IgA	k	47,XY,+8[20].	+8	Normal	
31	2/7.6/105	1.5	4.5	12.5	IgG	I	47,XY,del(5)(q22q35),+8[2]/46,XY[18]	-5q, +8	Polysomy 5, 9, and 15	
32	13/15.7/236	1.6	0.2	15	IgG	k	46,XX[20]	ND	ND	

CBC, Complete blood count; WBC, White blood cells ($\times 10^9/L$); Hb, Hemoglobin (g/uL); Plt, platelets ($\times 10^9/L$); PC, Plasma cells; Ig, Immunoglobulin; HC, Heavy chain; LC, Light chain; FISH, Fluorescence in situ hybridization; MDS, Myelodysplastic syndromes; PCM, Plasma cell myeloma; NA, Not applicable; ND, Not done; Mod, Moderate; RAEB, Refractory anemia with excess blasts; RCMD, Refractory cytopenia with multilineage dysplasia; AML, Acute myeloid leukemia; CMML, Chronic myelomonocytic leukemia. *Tested at the bone marrow with diagnosis of myeloid neoplasms.

obtained partial remission. DNA hypomethylating agents remained the main therapy for patients with MDS in our study. Twenty-six patients (81%) received single-agent azacitidine or lenalidomide or both with or without additional other agents (**Table 1**), and 3 patients (9%, patients 10, 19, and 27) were treated with growth factor(s) only. The patients who had disease transformation to AML were administered standard chemotherapy with 7+3 cytarabine (7 days) and an anthracycline (daunorubicin, 3 days) or CLAG-M (cladribine, cytarabine, mitoxantrone, and granulocyte colony stimulating factor).

During follow-up (median of 20 months; range, 2-143 months), 10 patients (31.25%) died of the disease. Of these patients, 2 had concomitant *de novo* AML with PCD (1 MGSU and 1 SMM), 5 had transformed AML from MDS, and 1 patient (patient 14) died from concomitant lung cancer. There were 2 additional patients with low-risk MDS who died of lung cancer. Because of the limited number of patients and overall short follow-up, statistically significant overall 5-year survival and progression-free survival rates based on IPSS risk stratification could not be determined (data not shown).

Cytogenetic and molecular findings

Conventional cytogenetic analysis with karyotyping was performed in 29 patients at the time of diagnosis. Sixteen patients (55%) had normal karyotype, 2 patients (7%) had complex cytogenetic abnormalities, 1 patient (3%; patient 17) had balanced translocation of *inv(16)(p13q22)*, and 10 patients (34.5%) had other cytogenetic abnormalities, including -5q, -20q, -Y, and +8. All of the cytogenetic abnormalities were classically associated with myeloid neoplasms and therefore most likely represent the myeloid diseases rather than PCD. Two of the patients (patients 12 and 21) with MDS had no documented cytogenetic study performed at the time of diagnosis. Based on IPSS score regarding cytogenetic risk groups in the MDS group [25], 65% had karyotypes associated with good prognosis, including normal karyotype (10 patients), *del(5q)* (1 patient), *del(20q)* (1 patient), and -Y (1 patient). We also found that 20% of the MDS patients had karyotypes with intermediate prognosis, including *i(17q)* (1 patient), combined *del(20q)* and monosomy 22 (1 patient),

combined *del(5q)* with +8 (1 patient), and trichloronal abnormalities (+8, -5, *t(3;5)*) (1 patient); 5% of patients had complex karyotype associated with poor prognosis. Chromosomal 7 abnormalities associated with poor prognosis were not detected at the time of diagnosis in the MDS patients.

Seven patients (35%) with MDS showed disease progression to AML (patients 4, 6, 7, 12, 15, 25, 29), with 2 of the 7 patients (29%; patients 4 and 29) displaying cytogenetic progression at the time of transformation to AML with acquisition of monosomy 7. There was one patient (patient 12) who had no documented cytogenetic finding at the time of diagnosis of MDS and showed intermediate cytogenetic findings of *del(16q)* and *del(20)* at the time of transformation to AML. Karyotypes were available in 6 of the 7 patients with initial diagnosis of AML, mostly indicating good prognosis, including 1 patient with recurrent cytogenetic abnormality, *inv(16)* (patient 17), 1 patient with loss of chromosome Y (patient 22), 1 patient with normal karyotype (patient 11), 1 patient with +8 (patient 30), 1 patient with complex karyotype (patient 26), and 1 patient with AML who had intermediate prognosis (patient 13). This patient later relapsed with a complex karyotype. The 3 patients with CMML showed normal karyotype (2 patients) and +8 (1 patient). FISH studies for MDS confirmed the cytogenetic abnormalities detected by conventional karyotype in all cases.

FISH studies with a panel of probes for plasma cell myeloma were performed for 15 patients. Compared with plasma cell myeloma in general [26, 27], there was a high frequency of normal FISH findings (40%, 6 patients) in this cohort. Four of 15 patients (27%) had unfavorable risk FISH abnormalities, including 1 patient with *t(4;14)* and gains of 1q21 and 3 patients with gains of 1q and/or *del(17p)*. Of note, the patients with poor risk FISH findings were identified as MGUS (patient 9) and SMM (patients 8, 20, and 29) (**Table 2**).

Discussion

Concomitant occurrence of different hematopoietic neoplasms has been well documented with the classic example being systemic mastocytosis with associated clonal hematopoietic non-mast-cell lineage disease incorporated

into the 2008 WHO classification of Tumors of Hematopoietic and Lymphoid Tissues [23]. To date, the majority of reported cases of myeloid neoplasms, especially AML and MDS associated with plasma cell dyscrasia, are secondary, developing as a consequence of prior cytotoxic chemotherapy such as melphalan with or without lenalidomide maintenance therapy in multiple myeloma [17]. Furthermore, dynamic MDS-associated molecular events were reported after high-dose melphalan autologous stem cell transplant associated with the total therapy treatment of multiple myeloma [28]. Only a limited number of cases of concomitant *de novo* myeloid neoplasm and PCD have been reported in the literature with myeloid neoplasms including chronic myelogenous leukemia [29] [30], AML [31-41], MDS [42-44], and BCR-ABL1 negative myeloproliferative neoplasms [45]. The myeloid disease and PCD appear to be clonally unrelated based on the few cases where clonal relationship was investigated. Two population-based studies of large cohorts of MGUS demonstrated significantly increased risk of development of MDS in untreated patients with MGUS [21, 22], suggesting a possible pathogenetic, etiologic, or microenvironmental association between the development of concomitant myeloid disease and PCD. In our cohort, there was a predominance of MDS (63%) and AML (22%), and most patients with MDS (75%) had low/intermediate-1 risk based on IPSS, similar to results reported in an international MDS study (71.5%) [46]. Yoshida and associates observed relatively low karyotypic risks in their series of 14 patients with MDS accompanied by MGUS [42]. Similarly, most of our MDS patients (70%) also had karyotypes associated with good prognosis. The most frequent cytogenetic finding was normal karyotype, and other cytogenetic changes were heterogeneous including -5/5q, -20q, +8, and i(17q) in our study. The notable exception was the absence of -7 or -7q in all MDS patients at the time of diagnosis. However, lacking such a high-risk cytogenetic aberration did not alter the natural history of MDS in our study. The overall rate of progression to AML was 35%, similar to that of the general population of MDS patients [46]. It is assumed that underlying dysregulated gene profiles that occurred at the stem cell level may play a leading role in the disease progression, which is worthy of exploration. Whether the PCD reported herein also

play a role in disease development or progression of myeloid neoplasm is still unclear. Initially, the subclinical PCD could just be a bystander in the setting. During disease development, the existing PCD clone could become a "competitor" or "inducer" for myeloid neoplasm. Clinical surveillance and treatment should focus on myeloid neoplasms given the low rate of disease progression of MGUS and/or SMM as a natural history [47]. It is assumed that the subclinical PCD-related clone may be suppressed during MDS/AML treatment in that some hypomethylating agents (e.g., lenalidomide used for MDS) can have a negative effect on PCD cells [48]. Lenalidomide could result in an alteration of bone marrow microenvironments via modulation of ubiquitin ligase function or proinflammatory cytokine release and further eliminate the clones [49]. In some occasions, unpredicted clonal expansion of plasma cells during the treatment of myeloid neoplasm could occur, likely attributed to interclonal competition.

Our cohort showed fairly equal number of MGUS (47%) and SMM (53%). None of the patients had lytic bone lesions or myeloma-associated end-organ damage. The anemia and peripheral cytopenia can mainly be attributed to the concomitant myeloid neoplasms. Clinically, it should also be an alert for a concomitant myeloid neoplasm when cytopenia is not proportional to the level of plasma cell infiltrate (<20%) in the bone marrow. Careful examination of bone marrow, in conjunction with molecular study, is necessary for an early detection of clonal myeloid neoplasm. In addition, given the asymptomatic nature of the MGUS and SMM in our series, patients with PCD in the presence of concomitant myeloid neoplasm could be underestimated in practice. The presence of M spike by serum protein electrophoresis and immunofixation should warrant further clinical, imaging, and bone marrow study including flow cytometry and immunohistochemical stains for plasma cell population.

FISH analysis with myeloma-specific probes demonstrated only a subset of patients (27%) harboring poor-risk FISH abnormalities. In contrast to the common course of patients with such FISH abnormalities (e.g., those with t(4;14), 1q gains, or del(17p) who often have a rapid disease progression or resistance to conventional therapy) [50], the small group of

patients (patients 8, 9, 20, and 29) in our study, for uncertain mechanisms, remained with an indolent clinical course and did not develop myeloma-associated end-organ damage or lytic bone lesions. Clinically, these patients could have benefitted from mainstream treatment, including azacitidine, for their myeloid neoplasms (Table 1). Regardless, for the 4 patients having a low plasma cell tumor load and not carrying any additional myeloid-related cytogenetic aberrations, such an appropriate treatment is recommended to prevent adverse outcomes.

Because of the indolent nature of the PCD in our study, only a few patients in our cohort received myeloma-specific therapy. It was considered that the mortality was due to the concomitant myeloid neoplasms. A study indicated that it is rare for patients with concomitant neoplasms to die from myeloma-associated end-organ damage [36]. Evidence is emerging that medication used in MDS (e.g., lenalidomide) could still benefit PCD, even with poor cytogenetic abnormalities [48]. According to our single institution experience, focusing therapy on the myeloid neoplasm and taking a watch-and-wait approach for PCD, especially in the absence of bone or renal disease is recommended.

Studies on whether these concomitant neoplasms share a similar pathogenesis are scarce. Dysregulation of the body's immune system may play a role. There is growing evidence that immune dysfunction, especially T-cell-mediated myelosuppression, plays an important role in the pathogenesis of MDS in some patients [51]. Impaired immune function in patients with MGUS and PCD is well recognized to lead to increased risk of infection [52, 53]. Thus, it is hypothesized that the impaired immune function caused by MGUS/SMM leads to survival of the MDS clone and eventual phenotypic presentation of MDS. This hypothesis can also be used to explain the increased risk of myeloid neoplasms in patients with MGUS as shown by population-based studies [21, 22].

In summary, we present a series of uncommon concomitant *de novo* myeloid disease and PCD. These patients harbored predominantly myeloid-related clonal cytogenetic abnormalities that were mainly subcategorized as low risk

according to IPSS. The overall rate of progression to AML was shown to be similar that of the general population with *de novo* MDS in prior reports. The PCD followed a uniformly indolent path, and treatment should target the myeloid neoplasm in these patients.

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Disclosure of conflict of interest

None.

Address correspondence to: Ling Zhang, Departments of Hematopathology and Laboratory Medicine, H Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL, USA. Tel: 813-745-2852; Fax: 813-745-1708; E-mail: Ling.Zhang@moffitt.org; Kenneth H Shain, Departments of Malignant Hematology, H Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL, USA. Tel: 813-745-2852; Fax: 813-745-1708; E-mail: Ken.Shain@moffitt.org

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