

Rare coexistence of Multiple Myeloma with Essential Thrombocythemia: Report of two cases

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The association of multiple myeloma (MM), a lymphoproliferative neoplasm, with essential thrombocytosis (ET), a myeloproliferative disorder, though documented, is extremely rare (Table 1).¹⁻⁷ We present two case reports of patients with both MM and ET.

Case report

Case 1

An eighty-five year old African American male presented in November 1996 with generalized malaise and joint pains and on routine laboratory evaluation was observed to have a platelet count of $927 \times 10^9/L$. Physical exam was unremarkable with no palpable liver, spleen or lymph nodes. Initial labs revealed normal hemoglobin (Hb), hematocrit, reticulocyte count, total and differential white blood cell counts (WBC). Plasma ferritin level was 34.3 ng/mL, serum iron was 22 $\mu\text{g/dL}$ and total iron binding capacity (TIBC) was 271 $\mu\text{g/dL}$ with transferrin saturation of 22%. Thrombocytosis with occasional small platelet clumps was seen on peripheral blood smear. Bone marrow biopsy revealed non-fibrotic megakaryocytic hyperplasia with normal marrow iron stores and plasma cells. No cause for reactive thrombocytosis could be identified. There was no evidence of monoclonal protein spike on serum and urine protein analysis. Therapy with hydroxyurea (1000 mg/day) was initiated and continued for two years following which the patient was put on aspirin (325 mg/day). He was seen regularly till April 1999 when the platelet count was observed to be lower but not in the normal range. He did not return for follow up until January 2001 when he presented to the emergency department following a syncopal episode. Physical examination was unremarkable. Platelet count then was $419 \times 10^9/L$. During workup for syncope, a chest X-ray revealed multiple erosive expansile lytic lesions of the ribs. CT scans of the chest, abdomen, pelvis and brain did not reveal any primary or metastatic neoplasm. Serum protein electrophoresis showed an abnormal spike in the gamma globulin region (4.44 g/dL). M-protein in the gamma globulin region was also observed on urine electrophoresis. Quantitative serum immunoglobulin analysis demonstrated markedly elevated IgG (5450 mg/dL; normal 717 – 1411 mg/dL) and lambda chain (4850 mg/dL; normal 253 – 653 mg/dL) bands with decreased IgA (14 mg/dL; normal 78 – 391 mg/dL), IgM (36 mg/dL; normal 53 – 334 mg/dL) and kappa chain (110 mg/dL; normal 534 – 1267 mg/dL) regions. Bone marrow biopsy and aspirate revealed hypercellular marrow with 60% atypical plasma cells. The patient was diagnosed as IgG - lambda chain MM. He refused any treatment for his MM and was referred for hospice care.

Case 2

A fifty-four year old Caucasian male presented with a history of chronic foot ulcers and stasis dermatitis in October 1992. Platelet count was observed to be $900 \times 10^9/L$ with Hb of 14.0 g/dL and WBC of $5.19 \times 10^6/L$. Iron studies revealed plasma ferritin levels of 118.4 ng/mL, serum iron 44 $\mu\text{g/dL}$, TIBC 271 $\mu\text{g/dL}$ and transferrin saturation of 20%. Thrombocytosis was seen on peripheral blood smear. Bone marrow biopsy and aspirate showed megakaryocytic hyperplasia with normal marrow iron stores and plasma cells. No obvious cause

TABLE 1
Review of patients with multiple myeloma and essential thrombocythemia reported in the literature (including our series of two patients)

S No	Ref.	Age/ Sex	Initial diagnosis	Time interval	Therapy for initial disorder	Remarks
1	1	61 M	Concomitant	-	-	-
2	1	56 M	Plasmacytoma	7 yr	EBRT*	Concomitant ET & MM at 7 years
3	1	47 M	Concomitant	-	-	-
4	2	70 M	Concomitant	-	-	Both ET & MM responded to melphalan
5	2	66 F	ET	8 mo	Busulfan	Platelets normal when MM was diagnosed
6	3	78 M	Concomitant	-	-	-
7	4	66 M	ET	5 yr	Busulfan & hydroxyurea	Platelets normal when MM was diagnosed
8	5	83 F	ET	14 yr	Thiotepa	Platelets normal when MM was diagnosed
9	6	-	ET	3 yr	$\alpha\text{-INF}^{\text{a}}$ & $^{32}\text{P}^{\text{b}}$	-
10	7	30 F	ET	7 yr	Busulfan & hydroxyurea	-
11	Case 1	85 M	ET	5 yr	Hydroxyurea	Platelets normal when MM was diagnosed
12	Case 2	54 M	ET	3 yr	Hydroxyurea & dipyridamol	Platelets normal when MM was diagnosed

^a Highest platelet count reported
^b External beam radiation therapy
^c Interferon alfa
^d Radioactive Phosphorus - 32

for a reactive thrombocytosis could be identified. He was diagnosed as ET and started on therapy with hydroxyurea (1000 mg/day) and dipyridamol (225 mg/day). No monoclonal protein spike was identified on serum or urine protein analysis. His ET course was complicated by thrombosis of the superficial femoral vein in May 1994. He presented in March 1995 with pain in the left hip region. X-ray of the hip revealed an expansile lytic lesion involving the left ischium and acetabulum. Biopsy from the pelvic lesion demonstrated plasmacytoma. There were no lytic bony lesions elsewhere on bone survey, bone marrow biopsy did not reveal increased atypical plasma cells and serum and urine protein electrophoresis studies did not show a monoclonal protein spike. Platelet count was $509 \times 10^9/L$. He was diagnosed as solitary plasmacytoma of the bone and received external beam radiation therapy to his left pelvis. He remained disease free for six months when, in November 1995, a bone survey revealed increasing bone involvement in the form of multiple expansile lytic lesions involving the pedicles of thoracic vertebrae, right distal radius, left ischium and left acetabulum. Physical exam was unremarkable. Bone marrow biopsy and aspirate showed plasmacytosis consistent with MM with atypical plasma cells comprising around 40% of the marrow cellularity. An abnormal M-protein was observed in the gamma globulin region on serum protein (6.94 g/dL) and urine electrophoresis. Quantitative serum immunoglobulin analysis demonstrated markedly elevated IgG (7210 mg/dL; normal 717 – 1411 mg/dL) and kappa chain (9660 mg/dL; normal 534 – 1267 mg/dL) bands with decreased IgA (40 mg/dL; 78 – 391 mg/dL), IgM (43 mg/dL; 53 – 334 mg/dL) and lambda chain (73 mg/dL; 253 – 653 mg/dL) bands. The platelet count then was $328 \times 10^9/L$. He was started on combination chemotherapy with melphalan and prednisone for IgG - kappa chain MM. He achieved complete remission until January 1998 when he was detected to have increasing M-protein on quantitative serum immunoglobulin analysis and new lytic lesions on bone survey. The patient subsequently received multiple courses of combination chemotherapy with vincristine, doxorubicin and dexam-

ethasone for progressive MM. His disease course was complicated by congestive heart failure secondary to infective endocarditis and chronic renal failure secondary to MM. The patient succumbed to progressive MM in January 2000, four years and two months after the initial diagnosis of plasma cell neoplasm.

Comment

The reason for the association of MM with ET remains unclear. Though a chance occurrence of two hematological disorders in the same patient cannot be discounted, other pathogenetic mechanisms need to be explored.

One possible explanation for this association could be the development of a treatment related second neoplasm. Leukemic conversion in ET is well recognized and the use of aggressive chemotherapy has been shown to increase this risk further⁸.

Another hypothesis that could explain the association of MM and ET is the existence of a putative pluripotent neoplastic stem cell with the capacity to differentiate into both lymphoid and myeloid cells. Rashkind et al have demonstrated that ET involves pluripotent stem cells capable of differentiation to immunoglobulin producing B-lymphoid cells in addition to myeloid cells⁹. Serum monoclonal component without MM has been reported in 8.2 – 9.7 % patients with MPD, conversely, polycythemia vera (a MPD) has been associated with MM^{10,11} Evidence also suggests that MM may actually be derived from a more immature progenitor cell with the potential for multilineage differentiation. Studies suggest the possible involvement of early B cells and the expression of myelomonocytic, megakaryocytic and erythroid antigens by myeloma cells¹².

The cytokine interleukin-6 (IL-6) may provide a common link between MM and ET. It has been demonstrated that IL-6 is a potent human myeloma-cell growth factor and overproduction of this cytokine is considered to be an important component in the pathogenesis and progression of MM (13). IL-6 is known to promote megakaryocytopoiesis in vitro and raise platelet counts in vivo. The pathogenetic interactions between IL-6 and the putative pluripotent stem cell implicated in the

pathogenesis of MPD including ET needs to be established.

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References

1. Zimelman AP. Thrombocytosis in Multiple Myeloma. *Ann Intern Med* 1973; 78: 970-971.
2. Selroos O, van Assendelft A. Thrombocythemia and multiple myeloma: A report of two cases. *Acta Med Scand* 1977; 201: 243-247.
3. Nestler JE. Immunoglobulin D multiple myeloma with thrombocytosis. *Ann Intern Med* 1981; 94: 412.
4. Prosper F, Borbolla JR, Rifon J, et al. Coexistence of essential thrombocythemia and multiple myeloma. *Ann Hematol* 1992; 65: 103-105.
5. Arlen PM, Goldkland GA. Multiple myeloma after treatment of essential thrombocythemia. *South Med J* 1995; 88: 79-81.
6. Cobo F, Cervantes F, Martinez C, et al. Multiple myeloma following essential thrombocythemia. *Leuk Lymph* 1995; 20: 177-179.
7. Kelsey PR, Patel K. Essential thrombocythemia followed by multiple myeloma in the same patient. *Clin Lab Hematol* 1995; 17: 349-351.
8. Tefferi A. Risk based management in essential thrombocythemia. *Hematology* 1999;172-177.
9. Rashkind WH, Jacobson R, Murphy S, et al. Evidence for involvement of B lymphoid cells in polycythemia vera and essential thrombocythemia. *J Clin Invest* 1985;75:1388-1390.
10. Economopoulos T, Economidou J, Papageorgiou E, et al. Monoclonal gammopathy in chronic myeloproliferative disorders. *Blut* 1989;58: 7-9.
11. Fink L, Bauer F, Perry JJ. Coincidental polycythemia vera and multiple myeloma: case report and review. *Am J Haematol* 1993;44:196-200.
12. Epstein J, Xiao HQ, He XY. Markers of multiple hematopoietic-cell lineages in multiple myeloma. *N Engl J Med* 1990;322:664-668.
13. Gado K, Domjan G, Hegyesi H, et al. Role of interleukin-6 in the pathogenesis of multiple myeloma. *Cell Biol Int* 2000;24:195-209.