

Myelofibrosis With Myeloid Metaplasia And Antiphospholipid Syndrome: Coexistent Etiologies Of Pulmonary Hypertension And Coagulation Factor Ii And V Deficiencies

A Huaringa, G Tapia, A Darwish, S Kornblau

Citation

A Huaringa, G Tapia, A Darwish, S Kornblau. *Myelofibrosis With Myeloid Metaplasia And Antiphospholipid Syndrome: Coexistent Etiologies Of Pulmonary Hypertension And Coagulation Factor Ii And V Deficiencies*. The Internet Journal of Pulmonary Medicine. 2002 Volume 3 Number 1.

Abstract

We report the first case of myeloid metaplasia with myelofibrosis (MMM) associated with antiphospholipid syndrome (APS) causing pulmonary arterial hypertension (PAH) and coagulation factor V deficiency. Chronic thromboembolic distal PAH occurs in the context of MMM and APS. These procoagulant states may independently involve the arterial and venous system. Therefore, recurrent thromboembolism in thrombophilia associated with MMM and APS may coexist in the development of PH and coagulation factor deficiencies.

Abbreviations: MMM: Myeloid Metaplasia with Myelofibrosis; Antiphospholipid Syndrome: APS; Pulmonary Arterial Hypertension: PAH; Myeloproliferative Disorders: MPD.

BACKGROUND

Despite three decades of research, the pathophysiological basis of the association between clinical disease and antiphospholipid antibodies (aPL) remains uncertain. That aPL are associated with clinical disease in non-autoimmune patients supports the notion that the antibodies are pathogenic (1).

In 1986, Hughes et al. described a clinical syndrome (Antiphospholipid Syndrome, APS) that represents a vasocclusive disease with acute thrombotic episodes which may involve all organ systems (2,3). There seems to be correlation between the development of APS in elders with underlying chronic diseases, such as malignancies (4), as well as the occurrence of malignancy in aPL-positive patients (5).

The APS and myeloproliferative disorders (MPD) have been found to cause Pulmonary Arterial Hypertension (PAH) (6,7). Pulmonary Embolism (PE) may be the first manifestation of APS. The prevalence of PAH is 3.5% and 1.8% in Primary APS and Secondary APS, respectively. However, in chronic

thromboembolic PAH (CTPH) the prevalence of aPL is 10-20% (10). The association of PH with aPL was first reported in 1983 (11). Since this original communication, there have been other twelve reports describing this association, not only with systemic lupus erythematosus but also in the primary APS (10,12). In contrast, there are three case reports and two case series published on myeloid metaplasia with myelofibrosis (MMM) associated with PAH (6,8,13).

We wish to report the first case of coexistent MMM and APS associated with pulmonary hypertension and coagulation factor V deficiency.

REPORT OF A CASE

We report the case of a 76 year old, white, man, diagnosed with myeloid metaplasia with myelofibrosis (MMM) and thrombocytopenia for the past 16 years. The patient was initially treated with hydroxyurea and anagrelide for the last year and a half. His chief complaint was worsening dyspnea on exertion for the previous seven months, with an acute episode of shortness of breath treated as congestive heart failure five months prior to referral to our service. On admission to M D Anderson Cancer Center, the initial work up revealed systolic pulmonary artery pressure of 120 mmHg, fractional shortening of 49%, cardiac output of 2.1

Myelofibrosis With Myeloid Metaplasia And Antiphospholipid Syndrome: Coexistent Etiologies Of Pulmonary Hypertension And Coagulation Factor II And V Deficiencies

L/min, ejection fraction of 65%, negative myocardial perfusion scan, low-probability ventilation perfusion (VQ) scan, and negative doppler ultrasound of lower extremities. Additionally, patient referred 50-lb weight loss over the past few years. He denied fever, chills, and night sweats. His past medical history disclosed right-sided cerebrovascular accident and an episode of myocardial infarction within the past 3 years. Moreover, Primary hypothyroidism of unknown etiology and basal cell and squamous cell carcinoma of skin on forearms and face were diagnosed five months ago. He has had a 20 pack-year history of cigarette smoking but quit 35 years ago. He worked as brakeman at a railroad company.

Current medications include Diltiazem 240 mg qd, Potassium 10 mg qd, Furosemide 20 mg qd, Anagrelide 0.5 mg bid qod, Prednisone 10mg, and Levothyroxine 50 mcg qd. Patient received heparin but developed an allergic reaction. On physical examination, the patient was pale, thin, alert. Vital signs were stable, saturation 93% on room air. Actinic changes were noted on cheeks, livedo reticularis on four limbs. Enlarged lymph nodes on cervical, axillary, and inguinal regions. Bibasilar crackles in the lung, no clubbing or cyanosis, grade 3/6 systolic murmur along left upper sternal border with accentuated P2 were noted. Jugular venous distention of 5 cm at 30 . In the abdomen, marked hepatosplenomegaly. Pitting edema from knees down.

Earlier laboratory work up from previous months disclosed: prothrombin time (PT): 17.1 (9.4-12.0), activated partial thromboplastin time (aPTT): 36 (22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35), factor II: 68 (75-130), factor V: 49 (60-140), factor VII: 72 (50-150), factor X: 77 (65-140), factor IX: 136 (55-150), haptoglobin: 32mg/dL (0.32 g/L, normal: 0.43-2.12 g/L,), aPTT-LA (lupus anticoagulant): 76 (0-45), aPTT-LA mix (mixed with normal pooled plasma): 51.8 (0-49), dilute Russell's viper venom time (dRVVT): 47 (0-43), fibrinogen: 73 (170-460), and negative direct coombs. On admission, blood urea nitrogen: 34 mg/dL (12.1 mmol/L), creatinine (Cr): 1.6 mg/dL (141.4 umol/L), Cr clearance: 32 cc/min, potassium: 5.6 mEq/L (5.6 mmol/L), total bilirubin: 1.1 mg/dL, alkaline phosphatase: 64 IU/L (1.06 nKat/L, normal: 0.5 - 2.0 nKat/L), aspartate aminotransferase: 28 IU/L (0.467 unKat/L, normal: 0 - 0.58 nKat/L), alanine-aminotransferase: 14 IU/L (0.233 nKat/L, normal: 0 - 0.58 nKat/L), lactate- dehydrogenase: 10353 IU/L (172.6 uKat/L), PT: 16.6 (9.4-12.5), 1:1 PT (no incubation): 13.9

(control 12.7); aPTT: 39 (23-40). White blood cell count: 7.4 K/uL ($7.4 \times 10^9 /L$), neutrophils 79% (0.79), lymphocytes 16% (0.16), red blood cell count: 3.04 M/uL, platelet count: 486 K/uL ($486 \times 10^9 /L$), blasts 6% (0.06), large platelets, and peripheral smear: schistocytosis.

Bone marrow aspirate: Increased reticulin and collagen, leukoerythroblastosis, myeloid immunophenotype. Flow cytometry: myeloblastic, cytogenetics: del (20q). Rapid Plasma Reagin, HBcAb, HBsAg, HCVAb, and HIV-1/2: non reactive. ANA, RF, SCL-70, proteinase-3 and myeloperoxidase antibodies: negative.⁶⁷ Gallium scan: negative. CT of the chest: low lung volume, mediastinal lymph nodes, basal emphysema. Echocardiogram: mild concentric hypertrophy, dilated right and left ventricles. Pulmonary function tests: mild restrictive pattern.

COMMENT

We discuss the case of a patient with PAH of multiple etiologies, and report to the best of our knowledge the first case of APS and factor V deficiency associated with MMM.

The etiology of PAH in this case was not that of emphysema or interstitial lung disease as evidenced by minimal parenchymal involvement on imaging studies. However, negative perfusion lung scan and doppler ultrasound of lower extremities could not exclude the possibility of pulmonary microthrombosis^(6, 8). Thrombotic microangiopathy has been associated with APS^(10, 26), and MPD^(8, 18). In fact, recurrent pulmonary embolism is assumed to be the major cause of PAH in APS^(5, 10); and, thromboembolism secondary to thrombophilia (in MMM) is well described^(7, 8, 18).

Although titers of aPL were not available in our patient, the diagnosis of APS was satisfied by other major criteria. These major criteria were past episodes of vascular thrombosis (microangiopathic hemolytic anemia, myocardial infarction, and stroke), laboratory criteria complying with prolonged phospholipid-dependent coagulation tests (aPTT, dRVVT), failure to correct the prolonged coagulation time by mixing with normal pooled plasma (aPTT-LA mix, undiluted 1:1 PT), and exclusion of other coagulopathies⁽¹⁴⁾.

Other distinct clinical manifestations of APS may be represented in our patient as renal insufficiency and hypertension (HTN)^(19, 23). However, the macrovascular and microvascular, and renal complications in our patient may also be secondary to MMM^(16, 21). The frequency of vascular

Myelofibrosis With Myeloid Metaplasia And Antiphospholipid Syndrome: Coexistent Etiologies Of Pulmonary Hypertension And Coagulation Factor II And V Deficiencies

(30-40%) and tubulo-interstitial or glomerular involvement (10%) has been well reported in APS but not in MMM (^{7,19}). In APS, 23% of arterial occlusions are coronary, 50% are cerebral, 27% involve renal, retinal and pedal arteries, and 14-23% present as microangiopathic hemolytic anemia (⁷). In contrast, Xiao et al and Au et al reported the renal involvement in MMM and MPD to be 12% and 3.6%, respectively (^{21,22}). Direct organ infiltration by extramedullary hematopoiesis (EMH) usually seen in MMM occurs in the monocyte-macrophage system and less commonly in pleura, pericardium and kidney. EMH rarely causes end-organ damage (²⁰). Although no tissue samples were available, we believe that such late-onset HTN may be associated with MPD or APS-related nephropathy (²³).

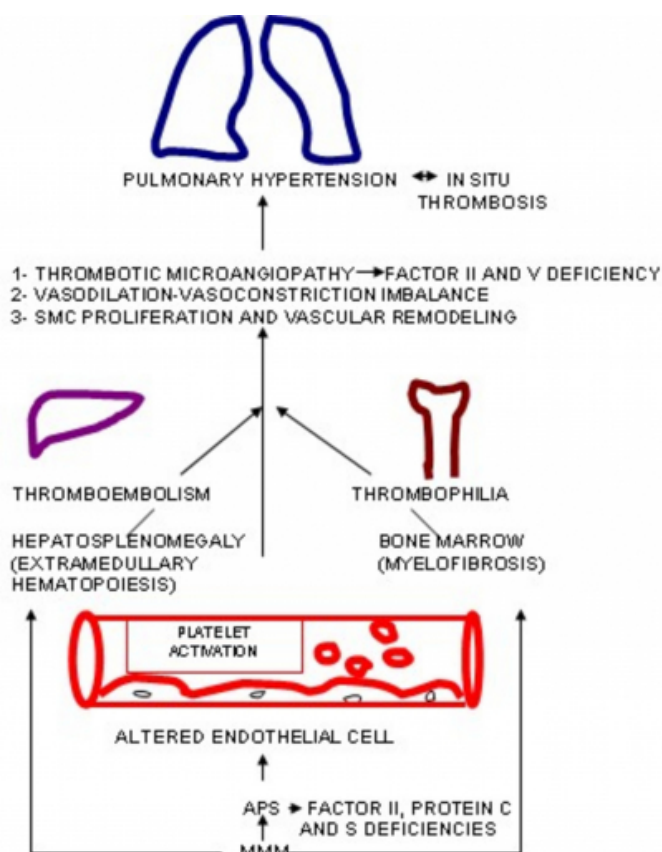
In terms of chronological presentation, we sustain that APS developed on the underlying MMM. It is believed that APS may be an insufficient force to generate thrombosis and a "second hit" such as MMM, immobilization, etc. may be necessary (⁷). Nevertheless, significantly higher rates of thromboembolic disease has been described in APS with or without cancer (⁵). We suggest a multifactorial origin (APS, MPD) in the development of PAH as well as the other vascular complications described in our case.

The proposed pathophysiology of thrombotic microangiopathy associated with APS and MMM supports the hypothesis of synergistic etiologies in PAH (Figure 1) (^{6,7}). In APS may exist antibody-dependent activation of endothelial cells (EC) with altered coagulation control and vasomotor tone, pulmonary vascular remodeling, release of endothelin-1, activation of platelets, and antibodies against oxidized-LDL (^{7,10,26}). The association of MPD with PH may be explained by platelet activation, thrombin generation, release of transforming growth factor- (TGF-) and platelet-derived growth factor (PDGF) both of which may cause smooth muscle hyperplasia, thromboxane release, chronic intravascular coagulation, severe hepatosplenomegaly, hyperviscosity, IgM-type monoclonal gammopathy accompanied by aPL positivity, disordered proliferative EC (present in cancer-related angiogenic processes), and leukemic infiltration of the lung (^{5,8,18,26,27}). Radioimaging studies did not support the presence of lung infiltration or pulmonary fibrosis associated with the use of hydroxyurea and anagrelide in our patient (⁸). Besides, portopulmonary hypertension is not favored in our case by the normal-sized azygos vein, normal liver function and low cardiac output (2.1 L/min).

Legend to figure 1: Pathophysiology of pulmonary arterial hypertension and coagulation abnormalities in myeloid metaplasia with myelofibrosis (MMM) associated with antiphospholipid syndrome (APS). SMC = Smooth Muscle Cell.

Figure 1

Figure 1: Pathophysiology of pulmonary arterial hypertension



Secondly, we wish to discuss the infrequent coagulation factor II and V deficiencies observed in our case. The negative past and family history of a hemorrhagic diathesis supports the belief that these deficiencies were acquired.

The synergistic effect of APS and MMM may again be seen in the decreased levels of prothrombin observed. This event may be related to the inhibition of prothrombin, up-regulation of tissue factor pathway, and thrombotic microangiopathy associated with APS (^{7,24}); and increased catabolism of prothrombin described in MPD (^{28,29}). In contrast, increased catabolism of fibrinogen and factor V have been reported in MPD (^{9,28,29}).

To the best of our knowledge, there is only one reported case of prothrombin deficiency secondary to myelofibrosis and

no report in reference to associated factor V deficiency (^{28, 29}). In contrast, in acute leukemias without liver involvement, factor V, X, and II deficiencies have been described (^{30,31}). Interestingly, the presence of rare, acquired inhibitors of factor V (circulating immunoglobulins) have been proposed in leukemias, and described in non-hematological or autoimmune diseases (^{30, 33}). In our patient, there were no assessments of possible circulating inhibitors; however, we sustain that multiple coexistent coagulation abnormalities exist and will be increasingly recognized.

Lastly, the possibility of deficient anticoagulant proteins exist in the context of recurrent thrombotic episodes seen in MPD. MPD have been associated with protein C deficiency (³⁴). In contrast, antibodies against protein C and S (implicated in phospholipid-protein complexes) have been demonstrated in the context of aPL (²⁴). Future studies will have a clarifying role in this matter.

The mild clinical improvement of our patient's dyspnea and pulmonary artery pressure (PAP), while on home oxygen therapy, calcium antagonists, and anagrelide, exemplifies how an established PAH becomes independent of the chronic thrombotic sources (⁸). The explanation lies on the existence of superimposed in situ thrombosis complicating all forms of severe PAH which is related to its duration (¹⁰). There are anecdotal reports on improved PAP levels with control of MPD (⁸).

SUMMARY

In summary, chronic thromboembolism seen in APS and thrombophilia associated with MMM may evolve into PAH and acquired coagulopathy. Coexistent procoagulant states in MPD challenge their increasing recognition in medical practice.

CORRESPONDENCE TO

Armando J. Huaranga MD, MHA, FACP, FCCP Associate Professor of Medicine Loma Linda University School of Medicine Medical Director, Critical Care Medicine White Memorial Medical Center 1720 Cesar E. Chavez Ave. Los Angeles, CA 90033 Email: huarinaj@wmmcpo.ah.org Telephone: 323.260.5802 Fax: 323.881.8761

References

1. Brighton TA, Chesterman CN. The clinical significance of antiphospholipid antibodies in patients without autoimmune disease. *Aust NZ J Med* 2000; 30: 693-703.
2. Hughes GRV, Harris EN, Gharavi AE. The anticardiolipin syndrome. *J Rheumatol* 1986; 13: 486-489.

3. Nochy D, Daugas E, Thi Huong DL, Piette JC, Hill GI. Kidney involvement in the antiphospholipid syndrome. *J Autoimm* 2000; 15: 127-132.
4. Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimm* 2000; 15: 145-151.
5. Asherson RA. Antiphospholipid antibodies, malignancies and paraproteins. *J Autoimm* 2000; 15: 117-122.
6. García-Manero G, Schuster SJ, Patrick H, Martinez J. Pulmonary hypertension in patients with myelofibrosis secondary to myeloproliferative disorders. *Am J of Hematol* 1999; 60: 130-135.
7. Levine JS, Branch DW, Rauch J. Medical progress: the antiphospholipid syndrome. *NEJM* 2002; 346: 752-763.
8. Dingli D, Útz JP, Krowka MJ, Ann LO, Tefferi A. Unexplained pulmonary hypertension in chronic myeloproliferative disorders. *Chest* 2001;120: 801-808.
9. Tefferi A. The Philadelphia Chromosome-Negative Chronic Myeloproliferative Disorders: A Practical Overview. *Mayo Clinic Proceedings* 1998; 73: 1177-1184.
10. Espinosa G, Cervera R, Font J, Asherson RA. The lung in antiphospholipid syndrome. *Ann Rheum Dis* 2002; 61: 195-198.
11. Asherson RA, Mackworth-Young CG, Boey ML, et al. Pulmonary hypertension in systemic lupus erythematosus. *BMJ* 1983; 287: 1024-5.
12. Rana M, Endo H, Watabe H, Tanaka S, Kondo H. A case of primary antiphospholipid syndrome complicated with pulmonary hypertension. *Ryumachi* 2001; 41: 869-74.
13. Weinschenker P, Kutner JM, Salvajoli JV, et al. Whole-pulmonary low-dose radiation therapy in agnogenic myeloid metaplasia with diffuse lung involvement. *Am J Hematol* 2002; 69: 277-280.
14. Wilson WA. Classification criteria for antiphospholipid syndrome. *Rheum Dis Clin N Am* 2001; 27: 499-505.
15. Tektonidou MG, Loannidis JP, Moyssakis, et al. Right ventricular diastolic dysfunction in patients with anticardiolipin antibodies and antiphospholipid syndrome. *Ann Rheum Dis* 2001; 60: 43-48.
16. Potti A, Rabadi KM, Willardsen DD. Thrombophilia in ischemic stroke. *West Journal of Medicine* 1998; 169: 385-6.
17. Arboix A, Besses C, Acin P, et al. Ischemic stroke as first manifestation of essential thrombocytemia. Report of six cases. *Stroke* 1995; 26: 1463-1466.
18. Leone G, Sica S, Chiusolo P, Teofili L, De Stefano V. Blood cells diseases and thrombosis. *Haematologica* 2001; 86: 1236-44.
19. Vlachoyiannopoulos PG, Kanellopoulos P, Tektonidou M, et al. Renal involvement in antiphospholipid syndrome. *Nephrol Dial Transplant* 2001, 16 [suppl6]: 60-62.
20. Woodward N, Ancliffe P, Griffiths MH, Cohen S. Renal myelofibrosis: an unusual cause of renal impairment. *Nephrol Dial Transplant* 2000;15: 257-8.
21. Au WY, Chan KW, Lui SL, Lam CC, Kwong YL. Focal segmental glomerulosclerosis and mesangial sclerosis associated with myeloproliferative disorders. *Am J Kidney Dis* 1999; 34: 889-93.
22. Xiao JC, Walz-Mattmuller R, Ruck P, Horny HP, Kaiserling E. Renal involvement in myeloproliferative and lymphoproliferative disorders. A study of autopsy cases. *Gen Diagn Pathol* 1997; 142: 147-53.
23. Cuadrado MJ, Hughes GRV. Hughes (antiphospholipid) syndrome. Clinical features. *Rheum Dis Clin NA* 2001; 27: 507-24.
24. Douglas A. Triplett. Antiphospholipid-protein antibodies: laboratory detection and clinical relevance. *Thrombosis Research* 1995; 78: 1-31.
25. Gossage JR. Primary pulmonary hypertension or

Myelofibrosis With Myeloid Metaplasia And Antiphospholipid Syndrome: Coexistent Etiologies Of Pulmonary Hypertension And Coagulation Factor Ii And V Deficiencies

- Portopulmonary hypertension?. *Chest* 1998; 114: 1224-5.
26. Tuder RM, Cool CD, Yeager M, Taraseviciene-Stewart L, Bull TM, Voelkel NF. The pathobiology of pulmonary hypertension. *Endothelium. Clinics in Chest Medicine* 2001; 22: 405-18.
27. Juby AG, Davis P. Prevalence and disease associations of certain autoantibodies in elderly patients. *Clinical and Investigative Medicine* 1998; 21: 4-11.
28. Mamiya S, Itoh T, Endo Y, Miura AB. Abnormal blood coagulation and fibrinolysis in chronic myeloproliferative disorders [Japanese]. *The Japanese Journal of Clinical Hematology* 1991; 32: 527-36.
29. Takahashi H, Hattori A, Shibata A. Profile of blood coagulation and fibrinolysis in chronic myeloproliferative disorders. *Tohoku J Exp Med* 1982; 138: 71-80.
30. Gralnick HR, Henderson E. Acquired coagulation factor deficiencies in leukemia. *Cancer* 1970; 26: 1097-101.
31. Pabinger-Fasching DI. Blood coagulation disorders in leukemia [German]. *Wien Med Wochenschr* 1991; 141: 213-216.
32. Weltermann A, Pabinger I, Geissler K, et al. Hypofibrinogenemia in non-M3 acute myeloid leukemia. Incidence, clinical and laboratory characteristics and prognosis. *Leukemia* 1998; 12: 1182-1186.
33. Feinstein D. Acquired Inhibitors of Factor V. *Thrombosis and Haemostasis (Stuttgart)* 1978; 39: 663-674.
34. Seitz R, Goke B, Egbring R, et al. Acute malignant myelofibrosis complicated by factor XIII deficiency, protein C decrease and skin necroses [German]. *Internist (Berl)* 1987; 28: 623-7.
35. De Stefano V, Teofili L, Rocca B, Nicoletti G, Leone G, Bizzi B. Association of congenital protein C deficiency and latent myeloproliferative disease as cause of splanchnic venous thrombosis in a 34-year-old woman. *Br J Haematol* 1989; 73: 565-6.

Author Information

Armando J. Huaringa, MD

Associate Professor of Medicine, Medical Director, Critical Care Medicine, Loma Linda University School of Medicine, White Memorial Medical Center

Gino G. Tapia, MD

Department of Blood and Marrow Transplantation, M.D. Anderson Cancer, University of Texas

Amr Darwish, MD

Department of Pulmonary Medicine, Menouffia University

Stephen M. Kornblau, MD

Department of Blood and Marrow Transplantation, M.D. Anderson Cancer, University of Texas