



Jugular vein thrombosis: a rare presentation of atypical chronic myeloproliferative disorder in a young woman

GIUSEPPE FAMULARO,* CLAUDIA PAPETTI,^o FRANCO CONTI,[#] NICOLA PETTI,^o FORTUNATO BLANDINO,^o CARLA RUSCIO,^o GIOVANNI MASCIOLI,[@] GIOVANNI BAROSI[^]

*Medicina d'Urgenza; ^oEmatologia, [#]Angiologia, [@]Anatomia Patologica, Ospedale San Camillo, Rome;

[^]Laboratorio di Informatica Medica, IRCCS Policlinico San Matteo, Pavia, Italy

ABSTRACT

Venous thromboembolism is common in subjects with chronic myeloproliferative disorders and is a recognized presenting feature of occult myeloproliferation. We report the case of a young woman who presented with acute thrombosis in the right jugular vein and pulmonary embolism. Splenomegaly and myeloid proliferation with bone marrow fibrosis, in the absence of the criteria for typical myeloproliferative disorders, allowed a diagnosis of an atypical form of chronic myeloproliferative disorder. This form carries a high risk of thrombosis and venous thromboembolism can be the presenting feature, though the course is often indolent. Acute thrombosis in the right jugular vein has not been so far described in these subjects. The outcome of young people with myelofibrosis is unpredictable, but a normal level of hemoglobin and the absence of blast cells and constitutional symptoms at presentation identifies subjects with a low probability of rapid disease progression.

©1999 Ferrata Storti Foundation

Key words: atypical myeloproliferative disorder, jugular vein thrombosis, myelofibrosis with myeloid metaplasia

A 23-year-old woman had a sudden onset of severe pain and swelling in the right side of her neck. On admission, the patient appeared well and her vital signs were normal. She was slim and muscular. Physical examination showed a right-sided neck swelling. A smooth, firm, fixed mass that was slightly tender and measured 3 x 5 cm was palpable on the right and extended into the supraclavicular fossa. The pulse of the right carotid artery was normal. The mass appeared to be distinct from the thyroid and was separate from the clavicle and there were no palpable breast masses or retractions. There were marked splenomegaly (12 cm in length from the splenic tip to the costal margin), but no hepatomegaly or lymphadenopathy. Auscultation of the

lungs revealed left basilar crackles without percussion dullness.

The differential diagnosis included primary lymphoma, primary neuronal tumor such as a glomus tumor of the carotid body, neurofibroma and, less likely, thyroid carcinoma or a metastatic neoplasm. The sudden onset of neck swelling and pain was considered to be not fully consistent with the hypothesis of a neoplasm. Furthermore, on the basis of the physical examination, the physicians caring for the patient agreed that cervical lymphadenopathy was not the cause of the mass. Axillary and inguinal lymph nodes were not enlarged, nor was the liver, despite the patient having a marked splenomegaly.

The patient's past medical history was unremarkable until six months prior to the admission when she was treated with empiric parenteral antibiotic therapy because of low-grade fever, cough productive of yellowish sputum, generalized malaise and a small, radiographically demonstrated left pleural effusion. Her pulmonary symptoms improved but did not disappear completely. Three weeks before admission to the hospital empiric parenteral antibiotic therapy was again administered because of a suspected pneumonia.

She had no chest pain, cough, fever, chills or night sweats. She had not lost weight in the preceding months, had no other medical problems and her family history was unremarkable. She did not smoke, drink alcohol or use illegal drugs; she also reported long-term use of oral contraceptives and denied high-risk sexual behavior. There was no history of occupational exposure to toxic compounds such as benzene, other solvents or pesticides.

The problem was, therefore, of a young patient with recurrent pulmonary symptoms. A diagnosis of recurrent pneumonia immediately came to mind, suggesting the possibility of an underlying immune deficiency. However, this patient had no risk factors for HIV infection and her family history did not support the suspicion of a primary immune deficiency syndrome. In addition, serum immunoglobulins, salivary IgA, absolute lymphocyte counts and CD4 and

Correspondence: Giuseppe Famularo, M.D., Dipartimento di Emergenza, Ospedale San Camillo, Circonvallazione Gianicolense, 00100 Rome, Italy. Phone & Fax: international +39-06-7847528 - E-mail: gfamularo@relay.uni.net

CD8 populations were measured two weeks before admission and reported to be in the normal range and a test for antibodies to HIV was negative. Lymphocyte responsiveness to mitogens and recall antigens was also normal and a skin test for tuberculosis with purified protein derivative (PPD) was negative. Other diagnoses, such as a primary neoplasm of the lung, systemic vasculitis with lung involvement, and a chronic granulomatous disease, including tuberculosis, were also considered but appeared unlikely. Thus, we were faced with a young woman presenting with a mass in the right side of the neck and marked splenomegaly after a brief history of possible recurrent pneumonia. However, laboratory evaluation ruled out primary immune deficiency and the patient was seronegative to HIV. Taking all the information into account, the hypothesis of recurrent pneumonia was greatly weakened.

Chest X-rays showed multiple small left and right lower lobe consolidations and a Doppler ultrasonography of the neck revealed a thrombus that occluded the right jugular vein and extended into the subclavian, innominate and superior cava veins (Figure 1). A ventilation-perfusion lung scan was highly suggestive of multiple segmental and subsegmental pulmonary emboli.

The only apparent risk factor this patient had for venous thromboembolism was the long-term use of oral contraceptives. There were no other acquired conditions that may precipitate venous thrombosis through increasing venous stasis or causing endothelial damage, such as surgery, trauma or immobilization, but the possibility of a hypercoagulable state associated with an occult blood neoplasm was again considered and the marked splenomegaly added weight to this hypothesis. Furthermore, the jugular vein is not a usual site of venous thrombus formation in long-term users of oral contraceptives. The possibility of a primary hypercoagulable state associated with anticoagulation protein deficiencies or anti-



Figure 1. Thrombus extending from the right jugular vein into the subclavian vein on Doppler ultrasonography.

phospholipid antibodies was also investigated. Physicians caring for the patient agreed to regard the two episodes of lung consolidation that this patient had experienced three weeks and six months, before admission as being caused by recurrent pulmonary thromboembolism rather than community acquired pneumonia.

Laboratory values were: hemoglobin 90 g/L, erythrocytes $4.22 \times 10^{12}/L$, white blood cells $7.8 \times 10^9/L$ with a normal differential count, and platelets $226 \times 10^9/L$. The prothrombin time and partial thromboplastin time, fibrinogen, antithrombin III, protein C and S levels were all within normal limits. Values for lactate dehydrogenase were elevated at 378 U/mL (upper limit of normal 240); D-dimer and fibrinogen split products (FSP) were increased as well (D-dimer: 2,600 ng/mL, normal < 200; FSP: 221 μ g/mL, normal < 10). The Leiden mutation of factor V was not present and assay for activated protein C resistance was normal. Autoantibodies, including antiphospholipid antibodies and lupus anticoagulant, were not detected and leukocyte alkaline phosphatase was normal. The erythrocyte sedimentation rate was also normal.

Blood levels of D-dimer, FSP and LDH were raised as commonly occurs in subjects with acute venous thrombosis and pulmonary embolism. Laboratory data ruled out a hypercoagulable state due to anticoagulant protein deficiencies or autoantibodies. The marked splenomegaly associated with a low hemoglobin concentration was of concern and, despite the normal erythrocyte sedimentation rate and the normal blood counts, further suggested a systemic process, possibly a blood cancer, as the underlying disorder in this patient.

A total-body computed tomography demonstrated a markedly enlarged spleen and slightly enlarged liver, but adenopathy or other masses were not found in the abdomen, chest or brain. A bone marrow aspirate showed prominent cellularity with normal maturation of erythroblastic and granuloblastic series and an increased proportion of megakaryocytes; there were fewer than 5% of blast cells. Bone marrow biopsy performed with a Jamshidi needle confirmed these findings and revealed a strongly increased reticulin and collagen fibrosis with no adipocytes (Figure 2). Peripheral blood smears did not contain teardrop-shaped, nucleated red cells, immature neutrophilic leukocytes, or abnormally large platelets. Chromosomal analysis showed a 46, XX karyotype and polymerase chain reaction for the ABL/BCR rearrangement was negative.

Leukemia and lymphoma were ruled out and we assumed that the patient had a myeloproliferative disorder with myelofibrosis presenting with acute venous thrombosis in the right jugular vein and pulmonary embolism. In view of the overlapping clinical features of myeloproliferative disorders, we excluded polycythemia vera because of the lack of erythrocy-

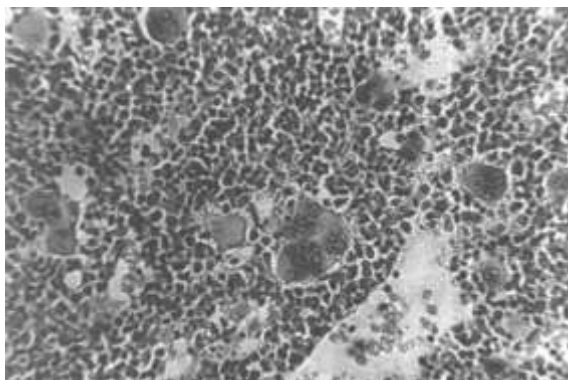


Figure 2. Prominent cellularity with normal maturation of hemopoietic series and increased reticulin and collagen fibrosis on bone marrow biopsy.

tos and an iron-replete state, chronic myelogenous leukemia because of the lack of the Philadelphia chromosome and essential thrombocythemia because of the lack of marked thrombocytosis. Secondary forms of myelofibrosis have been observed in association with a variety of neoplasms, infections and other diseases, as well as after toxic exposure to chemicals such as benzene. There was no indication in the case history of excessive exposure to benzene and no evidence on the basis of physical examination, laboratory data and imaging studies of infection or cancer. When myelofibrosis is secondary to infection, the infection is usually chronic, widespread, and easily diagnosed. Furthermore, with the availability of treatment for tuberculosis and the chronic fungal infections, myelofibrosis secondary to infection has become very unusual. In most cases associated with tumor, the tumor has already widely metastasized and thus it is easily recognized, although this is not always the case. The evolution of other myeloproliferative disorders into myelofibrosis with myeloid metaplasia is well known, being most commonly observed in polycythemia vera. Approximately 10 percent of these patients have a clinical syndrome indistinguishable from myelofibrosis with myeloid metaplasia.¹ However, our patient's laboratory data did not support this diagnosis because myelofibrosis with myeloid metaplasia resulting from one of the other myeloproliferative disorders is characterized by prominent leukoerythroblastosis (circulating immature white-cell and red-cell elements), marked dacryocytosis (teardrop red-cell forms), splenomegaly, which is frequently massive, and extensive marrow fibrosis.^{2,3}

The patient was treated with intravenous unfractionated heparin and warfarin and all symptoms gradually resolved. On day 38 after admission complete resolution of the lung consolidations and right jugular vein thrombosis was observed. A second ventilation-perfusion lung scan showed the complete dis-

appearance of the perfusion defects. After six months of follow-up the patient is doing well. She receives warfarin regularly as prophylactic treatment for a further thromboembolic event. Repeated blood counts and a bone marrow biopsy did not show any evidence of disease progression.

Discussion

Chronic myeloproliferative disorders can be found in subjects with venous thromboembolism, including deep vein thrombosis, pulmonary embolism, and Budd-Chiari syndrome.⁴⁻¹³

A major thrombotic event can be recognized early in the course of an atypical form of myeloproliferative disorder recently described in young people, and this can also be the presenting feature of those subjects.¹⁴ Thrombotic risk is one of the peculiar features of this atypical form of myeloproliferative disorder, together with splenomegaly, myeloid hyperplasia of the bone marrow, mild thrombocytosis and/or leukocytosis with rare immature myeloid cells in the peripheral blood, and a slowly progressive course.¹⁴ All patients described were younger than 46 years old. A major thrombotic event was the most frequent presenting feature and thrombotic complications, particularly in the portal system, intervened in the subsequent course in the majority of subjects.

In the young woman we report on the presence of a jugular vein thrombosis and pulmonary embolism heralded the presence of a chronic myeloproliferative disorder. The myeloproliferation was evidenced by splenomegaly, the presence of dysplastic megakaryocytes in the bone marrow, the prominent cellularity with normal maturation of the granuloblastic and erythroblastic series and increased reticulin and collagen fibrosis. A diagnosis of myelofibrosis with myeloid metaplasia was ruled out because of the absence of the diagnostic criteria recently proposed by the Italian Consensus Conference.¹⁵ The absence of teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes on peripheral blood smears, and the absence of clusters of megakaryoblasts in the bone marrow did not fit with the optional criteria to be met. The young age of the patient, and the presentation with acute venous thromboembolism supported the diagnosis of this atypical form of myeloproliferative disorder. This case was remarkable because of the most unusual site of acute thrombosis in the right jugular vein at presentation.

The long-term use of oral contraceptives by this patient certainly added to the risk of venous thrombosis but the relative contribution of oral contraceptive use cannot be established with confidence. This young woman had no inherited abnormalities of the coagulation system, such as the factor V Leiden mutation, which causes resistance to activated protein C, and deficiencies of antithrombin III, protein C, or protein S, that are associated with an increased risk of

venous thromboembolism in subjects on oral contraceptives.¹⁶ Since both the myeloproliferative disorder and the use of oral contraceptives cause hypercoagulability, it appears conceivable that their combination enhanced their individual effects on coagulation in this subject. Furthermore, even acquired abnormalities such as antiphospholipid antibodies were not found. The usual sites of thrombus formation in long-term users of oral contraceptives are the superficial and deep veins of the legs, but thrombosis may also occur in veins in the brain, retina, liver, and mesentery. We still do not know why venous thrombosis develops in the legs in some subjects and in other sites in others, but there is the possibility that patients with unusually sited thromboses have additional risk factors. In our patient, one might speculate that the long-term use of oral contraceptives in combination with a myeloproliferative disorder is a specific risk factor for thrombosis of the jugular vein.

The mechanisms accounting for the increased thrombotic risk carried by patients with myeloproliferative disorders have been investigated but remain incompletely understood. Clonal involvement of megakaryocytopoiesis resulting in abnormal platelet production is regarded as the main factor,^{12,17-19} however, at presentation our patient had a normal platelet count and platelets did not show morphologic heterogeneity or ultrastructural abnormalities. Peripheral blood mononuclear cells from subjects with myelofibrosis with myeloid metaplasia have a higher procoagulant activity than those of healthy individuals²⁰ and this probably contributes to the greater thrombotic risk even in those patients with a normal platelet count. An enhanced platelet sensitivity to thrombopoietin has also been implicated.^{19,21,22} Why the thrombotic events usually occur in the cerebrovascular district and portal system and the reasons for such a strong association with the Budd-Chiari syndrome are unexplained. Currently available laboratory parameters, such as platelet count or tests of platelet functions (platelet aggregation, generation of malondialdehyde, endogenous serotonin, β -thromboglobulin, and platelet coagulant activity), are of little help for predicting the risk of thromboembolic events in subjects with myelofibrosis with myeloid metaplasia as well as other myeloproliferative disorders.^{18,19} Furthermore, a rare syndrome of pseudothromboembolism has been described in patients with myeloid metaplasia.²³ In this disorder, islands of hematopoietic tissue are found in the pulmonary vasculature and may be clinically and radiographically indistinguishable from thromboembolism. Pseudothromboembolism appears unlikely in our patient for several reasons, including the good outcome following heparin treatment, prophylaxis of thrombotic events with warfarin and the close association of pulmonary embolism with acute thrombosis in the right jugular vein at presentation. Whether the previous episodes of probable recurrent pulmonary emboli were due to this

rare syndrome of pseudothromboembolism is uncertain.

Our patient had symptoms and findings consistent with a diagnosis of pneumonia and pulmonary thromboembolism was not considered until the thrombosis of the right jugular vein was found. Pulmonary symptoms in subjects with myeloproliferative disorders must always suggest the possibility of thromboembolic disease, even when other processes seem more likely. An aggressive diagnostic approach to rule out thromboembolism is justified in those subjects with even equivocal symptoms of thromboembolic disease.

The future outcome of the patient we reported on cannot be predicted with confidence. The clinical course of myelofibrosis in young individuals is variable, with some patients surviving for less than one year and others showing an indolent course. This makes it difficult to select candidates for hematopoietic stem cell transplantation, the only procedure carrying on the possibility of cure despite the significant morbidity and mortality associated with it. A recent study found that three variables at presentation (Hb < 10 g/dL, the presence of constitutional symptoms, and circulating blasts >30%) are each independently associated with shorter survival, allowing the identification of subjects with a high probability of an aggressive course of their disease.²⁴ Patients with at least two of those variables should be scheduled for transplantation as soon as possible. At presentation the patient we describe here had only one variable predictive of an aggressive course (Hb 9 g/dL) and, therefore, should be considered to be at intermediate or low risk of evolving disease. Indeed, the favorable outcome after six months of follow-up, with no evidence of disease progression or further thromboembolic events, indicates that the patient has an indolent form of the disease.

Splenectomy is also considered for the treatment of these patients, but it appears to be associated with an unexpectedly high incidence of blast transformation.²⁵

Contributions and Acknowledgments

GF and CP formulated the design of the study; GF, CP and GB wrote the paper; GF, CP, FC, NP and FB were responsible for clinical decisions and for data handling and analysis; CR was responsible for karyotype and BCR/ABL analysis; GM was responsible for the pathology review.

Criteria for the authors' name order: GF for clinical work, study conception and paper writing; CP for clinical work, study conception and paper writing; FC for clinical work; NP for clinical work; FB for clinical work; CR for karyotype analysis and BCR/ABL rearrangement; GM for pathology review; GB for study conception and paper writing.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received February 11, 1999; accepted June 8, 1999.

References

1. Landsaw SA. Acute leukemia in polycythemia vera. *Semin Hematol* 1986; 23:156-65.
2. Ward HP, Block MH. The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with myeloproliferative syndrome. *Medicine (Baltimore)* 1971; 50:357-420.
3. Manoharan A. Myelofibrosis: prognostic factors and treatment. *Br J Haematol* 1988; 69:295-8.
4. Reilly JT. Idiopathic myelofibrosis: pathogenesis, natural history and management. *Blood Rev* 1997; 11:233-42.
5. Cervantes F, Pereira A, Esteve J, et al. Idiopathic myelofibrosis: initial features, evolutive patterns and survival in a series of 106 patients. *Med Clin (Barcelona)* 1997; 109:651-5.
6. Cervantes F, Pereira A, Esteve J, et al. The changing profile of idiopathic myelofibrosis: a comparison of the presenting features of patients diagnosed in two different decades. *Eur J Haematol* 1998; 60:101-5.
7. Ozen S, Ferhanoglu B, Senocack M, et al. Idiopathic myelofibrosis (agnogenic myeloid metaplasia): clinicopathological analysis of 32 patients. *Leuk Res* 1997; 21:125-31.
8. Thiele J, Kvasnicka HM, Werden C, et al. Idiopathic primary osteo-myelofibrosis: a clinico-pathological study on 208 patients with special emphasis on evolution of disease features, differentiation from essential thrombocythemia and variables of prognostic impact. *Leuk Lymphoma* 1996; 22:303-17.
9. Hasselbach H. Idiopathic myelofibrosis: a clinical study of 80 patients. *Am J Hematol* 1990; 34:291-300.
10. Anger B, Seidler R, Haug U, et al. Idiopathic myelofibrosis: a retrospective study of 103 patients. *Haematologica* 1990; 75:228-34.
11. Pereira A, Cervantes F, Montserrat E, et al. Primary myelofibrosis: description of a series of 53 patients. *Med Clin (Barcelona)* 1989; 92:521-5.
12. Randi ML, Fabris F, Tison T, et al. Prevalence of specific thrombotic accidents in patients with thrombocytosis. *Haematologica* 1993; 25:149-52.
13. Cobo F, Cervantes F, Garcia-Pagan JC, et al. Budd-Chiari syndrome associated with chronic myeloproliferative syndromes: analysis of 6 cases. *Med Clin (Barcelona)* 1996; 107:660-3.
14. Barosi G, Buratti A, Costa A, et al. An atypical myeloproliferative disorder with high thrombotic risk and slow disease progression. *Cancer* 1991; 68:2310-8.
15. Barosi G, Ambrosetti A, Finelli C, et al. The Italian Consensus Conference on diagnostic criteria for myelofibrosis with myeloid metaplasia. *Br J Haematol* 1999; 104:730-7.
16. Olivieri O, Friso S, Manzato F, et al. Resistance to activated protein C in healthy women taking oral contraceptives. *Br J Haematol* 1995; 91:465-70.
17. Barbui T, Cortelazzo S, Viero P, et al. Thrombohaemorrhagic complications in 101 cases of myeloproliferative disorders: relationship to platelet number and function. *Eur J Cancer Clin Oncol* 1983; 19:1593-9.
18. Wehmeier A, Sudhoff T, Meierkord F. Relation of platelet abnormalities to thrombosis and hemorrhage in chronic myeloproliferative disorders. *Semin Thromb Hemost* 1997; 23:391-402.
19. Briere J, Kiladjian JJ, Peynaud-Debayle E. Megakaryocytes and platelets in myeloproliferative disorders. *Baillieres Clin Haematol* 1997; 10:65-88.
20. Bazzan M, Vaccarino A, Stella S, et al. Procoagulant activity of mononuclear cells is increased in myeloproliferative and myelodysplastic diseases. *Haemostasis* 1996; 26:157-63.
21. Ozaki S, Kosaka M, Ozaki K, et al. Thrombopoietin-responsive essential thrombocythemia with myelofibrosis. *Br J Haematol* 1997; 97:449-52.
22. Usuki K, Iki S, Endo M, et al. Influence of thrombopoietin on platelet activation in myeloproliferative disorders. *Br J Haematol* 1997; 97:530-7.
23. Gordon JJ, Austin M, Kurtides ES. Pseudothromboembolism in myeloid metaplasia. *Ann Intern Med* 1988; 108:837-8.
24. Cervantes F, Barosi G, Demory JL, et al. Myelofibrosis with myeloid metaplasia in young individuals: disease characteristics, prognostic factors and identification of risk groups. *Br J Haematol* 1998; 102:684-90.
25. Barosi G, Ambrosetti A, Centra A, et al. Splenectomy and risk of blast transformation in myelofibrosis with myeloid metaplasia. Italian Cooperative Study Group on Myelofibrosis with Myeloid Metaplasia. *Blood* 1998; 91:3630-6.