Primary Antiphospholipid Syndrome: A Cause of Fever of Unknown Origin

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Abstract

Antiphospholipid syndrome (APS) is defined as the occurrence of thrombosis, recurrent miscarriage, or both in association with laboratory evidence of persistent antiphospholipid antibodies. Owing to protean manifestations and laboratory studies, the diagnosis may be difficult. Because the other signs and symptoms of thrombosis are predominant, prolonged fever is not usually the main clinical finding. We describe a patient who presented with fever of unknown origin (FUO) and was found to have thromboses of the splenic vein, the superior mesenteric vein, and the portal vein due to the primary antiphospholipid syndrome. We also reviewed the medical literature (Medline 1966–2001), including the main FUO series of the previous 40 years, and laparotomy series for FUO. We conclude that although very rare, primary APS and thrombosis may present with FUO. APS should be considered in the differential diagnosis of prolonged fever associated with thrombosis. (Internal Medicine 42: 358–361, 2003)

Key words: fever of unknown origin, antiphospholipid syndrome, visceral thrombosis

Introduction

Antiphospholipid syndrome (APS) is defined as the occurrence of thrombosis, recurrent miscarriage, or both in association with laboratory evidence of persistent antiphospholipid antibodies (1–5). The thrombosis may affect both arteries and veins. In veins, deep-venous thrombosis is the most common manifestation, but involvement of visceral veins is well recognized (6). Because of the wide range of clinical manifestations and laboratory studies, the diagnosis

is difficult. The involvement of visceral veins may present with protean clinical manifestations (7). Because the other signs and symptoms of thrombosis are predominant, prolonged fever is not usually the main clinical finding. We describe a patient who presented with fever of unknown origin (FUO) and was found to have thromboses of the splenic vein, the superior mesenteric vein, and the portal vein due to the primary antiphospholipid syndrome. We also reviewed the medical literature (Medline 1966–2001), main FUO series of last 40 years (8–17), and laparotomy series for FUO (18–23).

Case Report

A 46-year-old man was admitted with abdominal pain, fatigue, anorexia, dark urine, diarrhea, and fever of 2 days. His past history was non-contributory. His elder brother had a history of myocardial infarction when he was 48. During admission, the temperature was 40°C, and he had jaundice on sclerae. Crackles over the left lower lung were significant. A chest X-ray revealed left lower lung atelectasis. Laboratory studies were as follows: hematocrit 36.3%, WBC 13,300/mm³ (granulocyte 83%, lymphocytes 9%, monocytes 8%), platelets 140,000/mm³, erythrocyte sedimentation rate 88 mm/h, CRP 219 mg/l (normal: 0–5), total protein 5.6 g/dl, albumin 3.1 g/dl, ALT 68 U/l, AST 64 U/l, γ -GT 118 U/l (7–47), alkaline phosphatase 297 U/l (64–306), total bilirubin 3 mg/dl with a direct fraction of 2.2 mg/dl. Urinalysis, thyroid hormones and abdominal ultrasonography were normal; aPPT was 49 seconds (normal: 29.4–39.8). Tuberculin skin test was negative. He was then prescribed ceftriaxone (2 g, i.v., daily) and clarithromycin (500 mg, i.v., twice daily), with a presumptive diagnosis of community-acquired pneumonia but his fever did not respond within 10 days. Three sets of blood culture (one obtained before antibiotherapy) remained sterile. *Mycoplasma pneumoniae* latex agglutination test, *Coxiella burnetii* antibodies (by complement fixation)

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Figure 1. Axial contrast-enhanced computed tomogram demonstrating hypodense filling defect in the portal vein (arrow head). Main biliary duct is not seen clearly at the neighborhood of the portal vein.

Figure 2. Axial contrast-enhanced section 4 months after the initial one revealing multiple small vascular structures around the portal vein (arrowhead). Portal vein diameter is decreased. There is no filling in the portal vein.

Legionella pneumophila antigen test (with ELISA) in urine, and *Leptospira* latex agglutination test remained negative. A thorax CT showed atelectasis of the posterobasal segment of the left lower lobe. Bronchoscopic examination was normal and microbiological studies (Gram and EZN staining and also cultures) of bronchoalveolar lavage fluid remained negative. D-dimer level was within normal limits. Although jaundice and pulmonary findings regressed within 10 days, fever persisted. Weil-Felix reaction and VDRL test remained negative. An abdominal CT revealed portal, splenic, and superior mesenteric thrombi, with an unclear biliary duct (Fig. 1). Amylase levels and also endoscopic cholangiography were normal. Lower extremity Doppler sonography, cranial MRI, and ophthalmic angiography were negative. Anti-nuclear and anti-DNA antibodies were not detected in serum. Lupus anticoagulant was negative. [This method stands on the principle that lupus anticoagulant is not absorbed by $\text{Al}(\text{OH})_3$ and withstands heating at 56°C . It also prolongs the partial thromboplastin time with Kaolin (24)]. Levels of protein C and antithrombin III were normal, Factor V Leiden mutation study remained negative; but anticardiolipin IgG was found as 22 GPL (0–8). [Anti-cardiolipin IgM [code GD27] and IgG [code GD26] were used. (Genesis Diagnostics, Cambridgeshire, United Kingdom). The method is for the detection of autoimmune anticardiolipin antibodies. It requires the presence of the co-factor β_2 -glycoprotein for binding]. The test repeated 10 days later resulted in 23.9 GPL. The fever persisted all 7 weeks. The patient was diagnosed as primary APS according to these results. He was administered low molecular weight heparin, which was switched to warfarin. He responded well; no fever was encountered after one week. Anemia of chronic disease type has improved, and abdominal CT after four months revealed multiple small vascular structures around the portal vein (Fig. 2). During a follow-up of 12 months, he is doing well. [Figure 3 shows

the interaction fever, therapy thrombosis and anticardiolipin titers]. A repeated Doppler sonography revealed chronic thromboses in portal vascular system and collaterals.

Discussion

Antiphospholipid antibodies are associated with a higher tendency to venous and arterial thrombosis. Primary APS seems to be much more common than expected with increased experience from anticardiolipin studies, clinical experience, and considering the syndrome in patients with otherwise unexplained thrombotic or thromboembolic events (7). It is a heterogeneous syndrome in terms of clinical manifestations. The establishment of the diagnosis may be difficult since antiphospholipid antibodies are encountered secondary to infections, in relation to drugs, and in some healthy individuals (1–3). However, the binding of the anticardiolipin antibodies from APS patients is β_2 -glycoprotein dependent (25); anticardiolipin antibodies from infectious patients can be distinguished from those found in autoimmune patients. The present patient had β_2 -glycoprotein-dependent anticardiolipin antibodies and the infectious diseases that may lead to detection of anticardiolipin antibodies were excluded.

The present patient presented with fever and pulmonary symptoms that led to a presumptive diagnosis of pneumonia. A CT of the thorax showed an atelectasis. Bronchoscopic examination was normal and microbiological studies of bronchoalveolar lavage fluid remained negative. Most probably these findings were consistent with pulmonary embolism. The clinical features of pulmonary embolism can be diverse and may range from no symptoms to sudden death. Chest pain, dyspnea, apprehension, and cough are the main symptoms. Tachypnea is the most common sign and rales are heard in nearly 60% of the patients (26). Among the chest

Figure 3. The relationship of fever, therapy and anticardiolipin levels. Temperature: mean of the highest body temperatures in a week in °C; weeks: weeks after admission of the patient, black arrow shows the initiation of the treatment; aCL-IgG: anticardiolipin-IgG, normal range of aCL-IgG: 0–8 GPL.

radiographic findings are focal oligemia, vascular enlargement, atelectasis, pleural effusions, and air space opacities representing pulmonary hemorrhage or infarction (27). A negative d-dimer of the present patient may not be against the diagnosis of pulmonary emboli: since we focused primarily on the pulmonary features of the case and considered it due to an infectious etiology, we have recognized portal thrombi in late time during the course. This corresponded nearly 30 days after the initiation of the symptoms. As shown by the study of Meissner et al (28), nearly 40% of the people with thrombi may have normal d-dimer levels at this time period.

Spirochetes *Leptospira* and syphilis were excluded serologically by *Leptospira* latex agglutination test and VDRL,

respectively. *Coxiella burnettii* antibodies (by complement fixation) were also negative. Among the other rickettsiae, Mediterranean Spotted Fever (due to *Rickettsia conorii*) is endemic in Turkey. During the last 8 years, we have followed 15 patients with MSF. The lack of clinical features [in particular, a maculopapular rash associated with fever and black spot (tache noire) and a negative Weil-Felix reaction] made this disease very unlikely.

Transient jaundice of the patient can be explained by the effect of thrombosed portal vein on the biliary system. Endoscopic cholangiography (performed after improvement of the jaundice) excluded a permanent biliary obstruction. Serology for viral hepatitis and liver biopsy excluded a parenchymal disorder. As seen on the abdominal CT pictures, the main biliary duct can not be seen in the vicinity of the enlarged, thrombosed portal vein. Jaundice due to portal venous thrombosis has been reported previously (29–31). Some patients with thrombosis may present with fever, and diagnostic difficulties may delay the establishment of the diagnosis: fever sometimes is associated with thrombosis. But since the other presenting signs and symptoms are generally more prominent and contributory to the diagnosis, a prolonged fever as the sole manifestation of thrombosis is rather rare. Kazmers et al (32) described fever in 16 out of 175 (9.1%) patients with deep venous thrombosis (DVT) defined as an oral temperature of $\geq 100^{\circ}\text{F}$ (37.8°C).

FUO was defined by Petersdorf and Beeson (8) as a temperature $>38.3^{\circ}\text{C}$ for a period of at least 3 weeks on several occasions and inability to reach a diagnosis after 1 week of inpatient investigation. The main diagnostic categories of FUO are infections, malignancies, collagen-vascular diseases, and other miscellaneous disorders.

In 10 major FUO series published within the last 40 years (8–17), including a total of 1,329 patients, only one patient described by Iikuni et al (15) had APS. This patient was not thoroughly discussed in this series of 153 patients, it was merely included in the list of the ones with fever lasting more than 3 months. Five described by Knockaert (12) had

Table 1. A Review of the Main FUO Series of the Last 40 Years

Number, (Reference number), Year	Total number of FUO cases	Cases with APS	Cases with thrombosis	Cases with pulmonary emboli
1, (6), 1961	100			
2, (7), 1977	100			
3, (8), 1982	105			
4, (9), 1992	218			
5, (10), 1992	199			5
6, (11), 1992	86		3	
7, (12), 1994	80			
8, (13), 1994	153	1		
9, (14), 1996	121			
10, (15), 1997	167			
Total	1,329	1	3	5

pulmonary emboli, and 3 described by Kazanjian et al (13) had thromboses. During the last 20 years (1982–2001) we have followed 130 patients fulfilling the criteria of FUO; none of the patients except the present case had APS or thrombosis.

AbuRahma et al (33) reported five patients of DVT diagnosed by venous duplex imaging of the lower extremities who met the criteria for probable cause of FUO. Patients with pulmonary emboli presented as FUO have also been reported (34).

When Doppler sonography or CT/MRI was not widely available, the laparotomy was the main method that would probably detect a visceral thrombosis. For this reason we reviewed 6 series of laparotomy for FUO including 75 patients; we did not find any patient with visceral thrombosis (18–23).

To conclude, although very rare, primary APS and thrombosis may present with FUO. Clinicians should consider APS in the differential diagnosis of prolonged fever associated with thrombosis.

References

- Greaves M. Antiphospholipid antibodies and thrombosis. (see comments) *Lancet* **353**: 1348–1353, 1999.
- Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. (see comments) *N Engl J Med* **332**: 993–997, 1995.
- Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* **346**: 752–763, 2002.
- Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. (editorial) *Br Med J (Clin Res Ed)* **287** (6399): 1088–1089, 1983.
- Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* **42**: 1309–1311, 1999.
- Hirohata Y, Murata A, Abe S, Otsuki M. Portal vein thrombosis associated with antiphospholipid syndrome. *J Gastroenterol* **36**: 574–578, 2001.
- Bick RL. Antiphospholipid thrombosis syndromes: etiology, pathophysiology, diagnosis and management. *Int J Hematol* **65**: 193–213, 1997.
- Petersdorf RG, Beeson PB. Fever of unexplained origin report on 100 cases. *Medicine* **40**: 1–30, 1961.
- Howard P, Hahn HH, Palmer RL, Hardin WJ. Fever of unknown origin: a prospective study of 100 patients. *Tex Med* **73**: 56–59, 1977.
- Larson EB, Featherstone HJ, Petersdorf RG. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970–1980. *Medicine* **61**: 269–291, 1982.
- Barbado FJ, Vasquez JJ, Pena JM, Arnalich F, Ortiz-Vasquez J. Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. *Postgrad Med J* **68**: 884–887, 1992.
- Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. *Arch Intern Med* **152**: 51–55, 1992.
- Kazanjian PH. Fever of unknown origin: review of 86 patients treated in community hospitals. *Clin Infect Dis* **15**: 968–973, 1992.
- Shoji S, Imamura A, Imai Y, et al. Fever of unknown origin: a review of 80 patients from the Shinetsu area of Japan from 1986–1992. (see comments) *Intern Med* **33**: 74–76, 1994.
- Iikuni Y, Okada J, Kondo H, Kashiwazaki S. Current fever of unknown origin 1982–1992. (see comments) *Intern Med* **33**: 67–73, 1994.
- Handa R, Singh S, Singh N, Wali JP. Fever of unknown origin: a prospective study. *Trop Doct* **26**: 169–170, 1996.
- de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). IA. Prospective multicenter study of 167 patients with FUO, using fixed epidemiology entry criteria. The Netherlands FUO Study Group. *Medicine (Baltimore)* **76**: 392–400, 1997.
- Martin RR. Exploratory laparotomy in fever unknown origin. *Md State Med J* **19**: 79–80, 1970.
- Barr J, Magnusson PH, Wallensten S. Laparotomy in cases of unexplained fever. *Acta Pathol Microbiol Scand [A]* **78**: 495, 1970.
- Howard PH, Hardin WJ. The role of surgery in fever of unknown origin. *Surg Clin North Am* **52**: 397–403, 1972.
- Moossa AR, Skinner DB. The place of laparotomy in the management of pyrexia of unknown origin. *Ann R Coll Surg Engl* **51**: 396–401, 1972.
- Rothman DL, Schwartz SI, Adams JT. Diagnostic laparotomy for fever or abdominal pain unknown origin. *Am J Surgery* **133**: 273–275, 1977.
- Takahashi T, Herrera MF, Onuma L, et al. Diagnostic laparotomy in fever of unknown origin. *Rev Invest Clin* **43**: 25–30, 1991.
- Pitney WR, Brozovic M. Quantitative assay of coagulation factors. in: *Practical Haematology*, Dacie JV, Lewis SM, Eds. International student edition of sixth edition, Edinburgh: Churchill Livingstone, 1984: 224–247.
- Sheng Y, Kandiah DA, Krilis SA. Beta2-glycoprotein I: target antigen for ‘antiphospholipid’ antibodies. Immunological and molecular aspects. *Lupus* **7 Suppl 2**: S5–9, 1998.
- Bell WR, Simon TL, DeMets DL. The clinical features of submassive and massive pulmonary emboli. *Am J Med* **62**: 355–360, 1977.
- Gotway MB, Edinburgh KJ, Feldstein VA, Lehman J, Reddy GP, Webb WR. Imaging evaluation of suspected pulmonary embolism. *Curr Probl Diagn Radiol* **28**: 129–184, 1999.
- Meissner MH, Zierler BK, Bergelin RO, Chandler WC, Manzo RA, Strandness DE Jr. Markers of plasma coagulation and fibrinolysis after acute deep venous thrombosis. *J Vasc Surg* **32**: 870–880, 2000.
- Bayraktar Y, Balkanci F, Ozenc A, et al. The “pseudo-cholangiocarcinoma sign” in patients with cavernous transformation of the portal vein and its effect on the serum alkaline phosphatase and bilirubin levels. *Am J Gastroenterol* **90**: 2015–2019, 1995.
- Nyman R, al-Suhaibani H, Kagevi I. Portal vein thrombosis mimicking tumour and causing obstructive jaundice. A case report. *Acta Radiol* **37**: 685–687, 1996.
- Khuroo MS, Yattoo GN, Zargar SA, et al. Biliary abnormalities associated with extrahepatic portal venous obstruction. (see comments) *Hepatology* **17**: 807–813, 1993.
- Kazmers A, Groehn H, Meeker C. Do patients with acute deep vein thrombosis have fever? *Am Surg* **66**: 598–601, 2000.
- AbuRahma AF, Saiedy S, Robinson PA, Boland JP, Cottrell DJ 4th, Stuart C. Role of venous duplex imaging of the lower extremities in patients with fever of unknown origin. *Surgery* **121**: 366–371, 1997.
- Wilson KH, Tuazon CU. Pulmonary emboli 5 days postinjury presenting as fever of unknown origin. *J Trauma* **20**: 259–261, 1980.