The Complexities of Anticoagulation in the Antiphospholipid Syndrome

Yair Levy MD and Maya Berla MD

Department of Medicine E, Meir Medical Center, Kfar Saba, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

In this issue of *IMAJ*, Podolak et al. [1] describe a patient with antiphospholipid syndrome and a history of catastrophic antiphospholipid syndrome who developed heparin-induced thrombocytopenia. Later, a scheduled kidney transplantation was delayed due to difficulty finding a safe and efficient anticoagulant.

CAPS, a severe variant of APS, is one of the devastating events that can occur in rheumatologic emergencies. It is characterized by clinical evidence of multiple organ involvement developing over a very short period, with histopathological evidence of multiple small vessel occlusions and laboratory confirmation of the presence of antiphospholipid antibodies, usually at a high titer. Although patients with CAPS represent less than 1% of all patients with APS, this is usually a life-threatening condition with 50% mortality.

The most common known trigger for CAPS is infection. Other less common causes are anticoagulation withdrawal or low international normalized ratio, medications (e.g., oral contraceptives), obstetric complications, neoplasia, systemic lupus erythematosus flares, trauma and surgery. Nevertheless, in almost half the cases, no obvious precipitating factors were identified and CAPS can often occur in patients with no previous thrombotic history. Treatment usually includes corticosteroids, anticoagulation, intravenous immunoglobulin, and plasma exchange [2,3].

Heparin-induced thrombocytopenia is one of the most important life and limb-threatening adverse drug events. It is described as an immune disorder associated with exposure to heparin. It occurs in approximately 2% of all patients who receive heparin (frequency differs by patient population), of whom approximately 35% develop thrombosis. The frequency of developing HIT antibodies, namely anti-platelet factor 4, can be very high (e.g., up to 40% in post-cardiac surgery patients). However, the presence of HIT antibodies does not necessarily correlate with clinical symptoms. Antibodies that are not associated with clinical symptoms have been termed "non-functional." However, although these might be functional antibodies, not all the conditions for the development of clinical symptoms have been met. HIT antibodies typically remain in circulation for 90 days [4-6]. HIT can occur both with the use of unfractionated heparin and less frequently with low molecular weight heparin.

Although they share some clinical features (including thrombocytopenia and thrombotic events), the association of APS with clinically apparent HIT is rare. Platelet factor 4 can be a common denominator in the pathogenesis of APS and HIT because PF4 tetramers can bind β2-glycoprotein I molecules. Artificially dimerized β2GPI molecules bind tightly to platelet membranes, activating them. It was found that PF4 assembled in homotetramers binds two molecules of β2GPI. This complex is recognized by anti-β2GPI antibodies and the entire complex is thrombogenic in terms of activating platelets, as confirmed by p38MAP kinase phosphorylation and thromboxane B2 production. Of note, PF4/heparin complexes are also immunogenic and trigger the production of anti-PF4/heparin antibodies, which activate platelets (the so-called heparin-induced thrombocytopenia and thrombosis syndrome). The anti-β2GPI antibodies activate platelets by their F(ab)2, while the anti-PF4/heparin activates platelets by their Fc fragments. Thus, PF4 is a common denominator in the pathogenesis of APS and HITT, which share clinical characteristics, such as thrombocytopenia and thrombosis [7].

A few studies have investigated the presence of anti-PF4 antibodies in patients with APS. Satoh et al. [8] investigated the prevalence and clinical correlations of anti-PF4 autoantibodies in 118 patients with SLE and in 27 with primary APS [8]. Heparin-dependent and independent anti-PF4 antibodies were measured with enzyme-linked immunosorbent assay. Antibody binding was confirmed to be heparin-dependent when inhibited by the presence of a high concentration of heparin. The presence of pathogenic anti-PF4 antibodies

CAPS = catastrophic antiphospholipid syndrome
APS = antiphospholipid syndrome

HIT = heparin-induced thrombocytopenia

PF4 = platelet factor 4
β2GPI = β2-glycoprotein I
HITT = heparin-induced thrombocytopenia and thrombosis syndrome

was assessed by serotonin-release assay. Heparin-dependent anti-PF4 antibodies were detected in 11 patients with SLE (9%). In serotonin-release assays, only the HIT sera induced platelet activation in vitro. Heparin-independent anti-PF4 antibodies were detected in 17 SLE patients (14%). There were no anti-PF4 antibodies in the sera of the primary APS patients. There was no correlation between the levels of heparin-dependent and independent anti-PF4 antibodies. Cross-reactivity between these two antibodies was not detectable by ELISA competitive assay. Heparin-dependent anti-PF4 antibodies were associated with thrombocytopenia and immunoglobulin M anticardiolipin ($P = 0.007$ for both comparisons), while heparin-independent anti-PF4 antibody levels were correlated with SLE disease activity index ($P = 0.0005$). None of the SLE patients with anti-PF4 antibodies had previous heparin exposure. The authors concluded that PF4 is an autoimmune target in SLE patients, and heparin-dependent and independent anti-PF4 autoantibodies might be involved in various pathophysiological aspects of SLE [8]. Pausner et al. [9] found in 32 of 42 patients (76.2%) with APS, APS and SLE, SLE, or SLE with antiphospholipid antibodies, that enzyme immunoassay IgG or particle gel immunoassay for PF4-heparin complex antibodies was positive [9]. Of these 32 samples, 26 (81.3%) tested positive for anti-PF4 antibodies. All 24 samples that were positive for PF4-heparin complex by EIA IgG were also positive for EIA IgG in the presence of excess heparin and all were negative by the heparin-induced platelet activation and heparin-induced platelet aggregation tests. They concluded that a large proportion of patients with APS and/or SLE have false-positive HIT antigen test results that are presumably related to autoantibodies against PF4, which can be distinguished from true

ELISA = enzyme-linked immunosorbent assay
SLE = systemic lupus erythematosus
Ig = immunoglobulin
EIA = enzyme immunoassay

HIT antibodies by EIA for PF4-heparin complexes tested with heparin excess, and by functional assays. Several case reports have mentioned a clinical association of APS with HIT, manifested as skin necrosis or other thrombotic events [10-19].

Patients with APS are usually treated with warfarin. If surgery is necessary, low molecular weight heparin or unfractionated heparin is administered a few days before the procedure, withdrawn right before it, and reinitiated immediately afterwards. For cases of APS associated with HIT, other drugs may be used. Treatment consists of alternative, non-heparin anticoagulants such as lepirudin (although its production was halted in 2012), argatroban, bivalirudin, danaparoid (danaparoid is not formally approved by the U.S. Food and Drug Administration for this condition) and fondaparinux. Each of these agents should be individually formulated based on the patient's parameters and the presence/absence of liver or renal failure [20].

Fondaparinux is a synthetic pentasaccharide that selectively binds antithrombin and causes rapid and predictable inhibition of factor Xa. It is rapidly absorbed (in < 30 minutes) after subcutaneous injection and its half-life permits dosing once a day. Therapeutic doses (5.0–10.0 mg subcutaneously) seldom induce prolonged activated partial thromboplastin time. Although plasma levels can be measured with an anti-factor Xa assay with a fondaparinux standard, routine anti-Xa monitoring is not required. Fondaparinux can initiate the formation of anti-PF4 antibodies; however, it generally does not support platelet activation by the newly formed immune complexes. Fondaparinux-associated heparin-induced thrombocytopenia has been described in a handful of patients. A few case reports have described its successful use in HIT associated with APS [13-15].

Danaparoid is a mixture of non-heparin, low molecular weight, sulfated glycosaminoglycans, including heparan sulfate, dermatan sulfate, and chondroitin sulfate. It causes long-acting antithrombin-dependent inhibition of factor Xa. In vitro cross-

reactivity of danaparoid with some of the antibodies that cause heparin-induced thrombocytopenia has been reported, but it is usually of only modest clinical significance. Monitoring for anti-Xa activity (calibrated for danaparoid) should be undertaken in patients whose body weight is outside the range of 55 to 90 kg and in patients with acute renal failure. A single report of successful danaparoid use in four children with APS and HIT has been published [16].

Argatroban is a direct thrombin inhibitor. It is administered intravenously and drug plasma concentrations reach steady state in 1–3 hours. Argatroban is metabolized in the liver and has a half-life of about 50 minutes. It is monitored by activated partial thromboplastin time. Because of its hepatic metabolism, it may be used in patients with renal dysfunction. It should not be used in patients with hepatic insufficiency and its effect on the prothrombin time/INR may complicate transition to long-term anticoagulant therapy with warfarin. In patients taking other hepatically cleared medications, lower initial doses may have to be used to avoid over-anticoagulation. Only one case report, of four patients with APS and HIT, has described the successful use of argatroban [17].

Bivalirudin is also a direct thrombin inhibitor. It has a unique pharmacologic profile: unlike other marketed direct thrombin inhibitors, it undergoes predominantly non-organ elimination (proteolysis) and has the shortest half-life (approximately 25 min) of all anticoagulants. Bivalirudin is only 20% metabolized via the renal system and requires only modest dose adjustments in patients with severe renal insufficiency; thus, it may be used in patients with advanced renal disease. In addition to the paper published here, two case reports describe the successful use of bivalirudin in patients with APS and HIT [18,19].

Finally, it is important to conduct thorough clinical and laboratory diagnoses of HIT in APS patients. An erroneous

INR = international normalized ratio

diagnosis might be fatal due to incorrect decisions regarding treatment [21].

To summarize, the case report of Podolak et al. presented in this journal adds important knowledge to the subject of controlling thrombosis in patients with APS accompanied by HIT. Additional case reports and controlled trials are needed to clarify the appropriate treatment options for this complex situation in APS.

Corresponding author:
Dr. Y. Levy
Dept. of Medicine E, Meir Medical Center, Kfar Saba 44261, Israel
Phone: (972-9) 747-2592
Fax: (972-9) 744-0085
email: levy.yair@clalit.org.il

References

1. Podolak B, Blickstein D, Inbal A, et al. Renal transplantation in a patient with catastrophic antiphospholipid syndrome and heparin-induced thrombocytopenia. *IMAJ* 2014; 16: 61-2.

2. Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. *Autoimmun Rev* 2010; 10: 74-9.

3. Sciascia S, Lopez-Pedrera C, Roccatello D, Cuadrado MJ. Catastrophic antiphospholipid syndrome (CAPS). *Best Pract Res Clin Rheumatol* 2012; 26: 535-41.

4. Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. *N Engl J Med* 2006; 355: 809-17.

5. Kelton JG, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. *Blood* 2008; 112: 2607-16.

6. Cuker A. Heparin-induced thrombocytopenia: present and future. *J Thromb Thrombolysis* 2011; 31: 353-66.

7. Vlachoyiannopoulos PG, Routsias JG. A novel mechanism of thrombosis in antiphospholipid antibody syndrome. *J Autoimmun* 2010; 35: 248-55.

8. Satoh T, Tanaka Y, Okazaki Y Kaburaki J, Ikeda Y, Kuwana M. Heparin-dependent and -independent anti-platelet factor 4 autoantibodies in patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2012; 51: 1721-8.

9. Pauzner R, Greinacher A, Selleng K Althaus K, Shenkman B, Seligsohn U. False-positive tests for heparin-induced thrombocytopenia in patients with antiphospholipid syndrome and systemic lupus erythematosus. *J Thromb Haemost* 2009; 7: 1070-4.

10. Yazbek MA, Velho P, Nadruz W, Mahayri N, Appenzeller S, Costallat LT. Extensive skin necrosis induced by low-molecular-weight heparin in a patient with systemic lupus erythematosus and antiphospholipid syndrome. *J Clin Rheumatol* 2012; 18: 196-8.

11. Ceriana P, Maurelli M, Locatelli A, et al. Pseudomyxoma of the right atrium in a patient with heparin-associated thrombocytopenia and antiphospholipid antibodies. *J Cardiothorac Vasc Anesth* 1995; 9: 308-11.

12. Gibson GE, Gibson LE, Drage LA, Garrett CR, Gertz MA. Skin necrosis secondary to low-molecular weight heparin in a patient with antiphospholipid antibody syndrome. *J Am Acad Dermatol* 1997; 37: 855-9.

13. Tokgoz H, Caliskan U, Demir M. Successful use of fondaparinux in a child with heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis* 2012; 23: 769-71.

14. Manco-Johnson MJ, Wang M, Goldenberg NA, et al. Treatment, survival, and thromboembolic outcomes of thrombotic storm in children. *J Pediatr* 2012; 161: 682-8.

15. Holtan SG, Knox SK, Tefferi A. Use of fondaparinux in a patient with antiphospholipid antibody syndrome and heparin-associated thrombocytopenia. *J Thromb Haemost* 2006; 4: 1632-4.

16. Zöhrer B, Zenz W, Rettenbacher A, et al. Danaparoid sodium (Orgaran) in four children with heparin-induced thrombocytopenia type II. *Acta Paediatr* 2001; 90: 765-71.

17. Pendleton R, Wheeler MM, Rodgers GM. Argatroban dosing of patients with heparin-induced thrombocytopenia and an elevated aPTT due to antiphospholipid antibody syndrome. *Ann Pharmacother* 2006; 40: 972-6.

18. Leissner KB, Ketchedjian A, Crowley R, Ortega R, Hesselvik JF, Shemin RJ. Deep hypothermic circulatory arrest and bivalirudin use in a patient with heparin-induced thrombocytopenia and antiphospholipid syndrome. *J Card Surg* 2007; 22: 78-82.

19. Cain RL, Spiess BD, Nelson M, Deanda A Jr, McCarthy HL, Green JA. Bivalirudin anti-coagulation for a patient with hypercoagulable immune syndromes undergoing mitral valve surgery. *Ann Thorac Surg* 2006; 81: 2308-10.

20. Kelton JG, Arnold DM, Bates SM. Nonheparin anticoagulants for heparin-induced thrombocytopenia. *N Engl J Med* 2013; 368: 737-44.

21. Smythe MA, Warkentin TE, Woodhouse AL, Zakalik D. Venous limb gangrene and fatal hemorrhage: adverse consequences of HIT "overdiagnosis" in a patient with antiphospholipid syndrome. *Am J Hematol* 2011; 86: 188-91.

"What is life? It is the flash of a firefly in the night. It is the breath of a buffalo in the wintertime. It is the little shadow which runs across the grass and loses itself in the sunset"

Crowfoot (1821-1890), Native American warrior and orator

"Show me a hero and I will write you a tragedy"

F. Scott Fitzgerald (1896-1940), American novelist widely regarded as one of the greatest American writers of the 20th century. Fitzgerald is considered a member of the "Lost Generation" of the 1920s. He wrote four novels: *This Side of Paradise*, *The Beautiful and Damned*, *The Great Gatsby* (his most famous), and *Tender Is the Night*