Familial antiphospholipid syndrome presenting as bivessel arterial occlusion in a 17-year-old girl

Jelušić, Marija; Starčević, Katarina; Vidović, Mandica; Dobrota, Savko; Potočki, Kristina; Banfić, Ljiljana; Anić, Branimir

Familial antiphospholipid syndrome presenting as bivessel arterial occlusion in a 17-year old girl

Marija Jelušić[1], Katarina Starčević[1], Mandica Vidović[1], Savko Dobrota[2], Kristina Potočki[2], Ljiljana Banfić[3] , Branimir Anić[4]

[1] *Department of Paediatrics, Division of Paediatric Rheumatology and Immunology, University Hospital Center Zagreb, Zagreb, Croatia*

[2]*Department of Diagnostic and Interventional Radiology, University Hospital Center Zagreb, Zagreb, Croatia*

[3]*Department of Cardiovascular Disease, University Hospital Center Zagreb, Zagreb, Croatia*

[4]*Department of Internal Medicine, Division of Immunology and Rheumatology, University Hospital Center Zagreb, Zagreb, Croatia*

Correspondence to:

Marija Jelušić

Department of Paediatrics, Division of Paediatric Rheumatology and Immunology, University Hospital Zagreb,Univeristy of Zagreb School of Medicine

Kišpatićeva 12, 10000 Zagreb, Croatia

Tel: ++385-1-2388-701

Fax: ++385-1-2421-894

E-mail: marija.jelusic.drazic@gmail.com

Abstract:

This article presents a case of a 17-year old girl with primary antiphospholipid syndrome developing subacute signs of hand and leg ischaemia caused by radiologically verified radial and popliteal artery occlusion. She is successfully treated with a thrombolytic agent (alteplase) and recovers completely. Her laboratory results came positive for all three subtypes of antiphospholipid antibodies. This kind of antiphospholipid syndrome presentation is a very rare entity in itself. Shortly afterwards her mother is diagnosed with primary antiphospholipid syndrome as well. A familial form of antiphospholipid syndrome is suspected. Combination of a familial antiphospholipid syndrome presenting as bivessel arterial thrombosis is a unique case, to the best of our knowledge, never described in the literature before.

Keywords:

Familial Antiphospholipid Syndrom; Child; Peripheral arterial disease; Thrombosis, etiology; Antibodies, antiphospholipid

Abbreviations:

APS: antiphospholipid syndrome; aPL : antiphospholipid; aCL: anti-cardiolipin; β_2-GPI: β_2-glycoproteinI; LAC: lupus anticoagulant; SLE: systemic lupus erythematosus; CAPS: catastrophic antiphospholipid syndrome; LWMH: low-molecular weight heparine; ANA: antinuclear antibodies; DVT: deep vein thrombosis

Introduction:

Antiphospholipid syndrome (APS) is an autoimmune multisystem prothrombotic disorder which by definition presents itself with thromboembolic events and positive laboratory tests for antiphospholipid (aPL) antibodies [1]. There is a whole panel of aPL antibodies, but only three types are included in the diagnostic criteria and are standardized worldwide. These are antibodies against cardiolipin (aCL), β_2-glycoprotein I (β_2-GPI) and the lupus anticoagulant (LAC) [2].

Antiphospholipid syndrome is also known as the Hughes syndrome and is usually divided into three groups: the primary APS, APS associated with systemic lupus erythematosus (SLE) or some other lupus-like connective tissue disorder (formerly known as the secondary APS) and the so-called catastrophic antiphospholipid syndrome (CAPS), a rare form of APS which leeds to disseminated intravascular coagulation causing rapid death [3]. For the adult population, there are international diagnostic criteria which were last time revised in 2007 [2]. They include at least one clinical thrombotic manifestation and at least one persistently positive aPL antibody (positive on two or more occasions at least 12 weeks apart). Clinical guidelines for adult APS include obstetric problems as well, most commonly recurrent miscarriages [2]. Internationally standardized classification and guidelines had not yet been made for the paediatric population. When diagnosing APS in a child, one is left only with modified adult criteria. Nevertheless, the majority of APS characteristics are the same [4].

Case presentation:

We present a 17-year old Caucasian who is transferred mid- December 2009 to our hospital with signs of subacute limb ischaemia and a sonographically raised suspicion of a left popliteal and right radial artery occlusion. Her symptoms began mid-November with itchiness and rash of the little finger of the right hand and then with pain, cyanosis and paresthesia of her left toe, progressing to the whole left lower leg. Because of irregular menstrual cycles, she had been using oral contraceptives (Logest – composed of gestoden and ethinylestradiol) for three months up to the moment presented symptoms occured. First, she was admitted to a local hospital under the suspicion of acute limb ischaemia. Right radial artery and left popliteal artery occlusion were sonographically verified and the girl was started on low molecular weight heparine (LWMH) – Clivarine and stopped using oral contraceptives. A partial improvement was noted.

Then she was referred to our Department for further therapeutic and diagnostic procedures considering APS or vasculitis as the underlying disorder. On admission, she reported pain in the left popliteal fossa. Her right radial pulse was feable and arteries distal to the common femoral artery on the left leg couldn't be palpated. A non-specific non-blanching rash was noted on her right hand. Her laboratory results showed slightly elevated d-dimers, slight thrombocytopenia and anaemia. Other than that, her blood tests and complete metabolic panel didn't show any significant pathologic findings. Her prothrombotic test panel came positive for LAC and showed elevated titers of aCL (both IgG and IgM) and

particularly anti β_2-GPI. Other results for coagulation disorders came back negative (FV mutation, FII mutation,PAI mutation, protein S, protein C, F VIII, F IX, F X activity).

Day after admission, here limb ischaemia symptoms reoccured. An urgent digital subtraction angiogram (DSA) was performed with concurrent alteplase thrombolytic therapy being conducted (**Fig.1** Angiogram showing occlusion of the popliteal artery prior to the thrombolytic therapy, the distance x1 indicating the length of the arterial occlusion). Shortly after the thrombolytic therapy, her symptoms subsided and the control angiogram showed significant improvement, although initially, there persisted some patency problems (**Fig.2** Angiogram performed six hours after the thrombolysis, still showing some patency problems of the popliteal artery). The same were absent on the subsequent angiograms (**Fig.3** Angiogram performed 42 hours after thrombolysis showing completely patent popliteal artery). Other than that, she was started on parenteral anticoagulation therapy until the sonographic findings, pletysmographic pulse - waves and ankle-brachial index didn't normalize completely.

End of December 2009, she was released from the hospital, completely recovered and with reccomendation of warfarin therapy. Repeated testing, performed more than 12 weeks later, showed persistently elevated aPL antibodies and persistently negative ANA, thereby confirming the diagnosis of primary antiphospholipid syndrome.

The mother of the girl was diagnosed with primary APS just months afterwards. She presented with simptoms of superficial thrombophlebitis and her blood tests showed elevated aCL, LAC and β_2-GPI on more than two occasions. She is

currently under surveillance for a possible progression into a secondary APS connected with SLE, considering her history of arthritides, dermatologic problems (livedo reticularis and exanthematous eruptions) and laboratory results showing slight leukopenia and persistently lowered whole complement activity. Her HLA typisation showed following genotype – HLA A 11/28, B 35/39, DR 11/16.

Beside the forementioned, the girl's family history includes father dying from consequences of a heart attack at the age of 45 years.

During subsequent follow-up, both the mother and the daughter remain positive for aCL antibodies and continue receiving oral anticoagulant therapy (warfarin).

Discussion:

We report a case of a 17-year old girl who presents with subacute hand and leg ischaemia. Soon after, radiological work-up reveals left popliteal artery and right radial artery occlusion which are successfully treated with thrombolytic – alteplase therapy. The girl's laboratory tests showed positive LAC and elevated aCL and anti – β_2-GPI, which, together with clinical findings fulfill criteria for APS diagnosis. She hasn't got any acquired prothrombotic risk factors except for a three-month history of oral contraceptive taking due to irregular menstrual cycles.

Paediatric APS extremely rarely presents with acute limb ischaemia. Our literature review came up with only one report of acute distal ischaemia as a presentation of antiphospholipid syndrome in a child [5], [6].

Additionally, the possibility of a familial APS makes this case report even more interesting, since it's not a common clinical entity. Namely, her mother developed thromboses and has elevated serum aPL-antibodies, and her father died of a myocardial infarction at the early age of 45. Mother is currently diagnosed with primary APS and is under futher monitoring in case she develops a connective tissue disorder.

Familial clusterings of raised levels of aPL antibodies have been described, but the reports are heterogeneous with regard to the characterization of the APS, coexisting autoimmune diseases and clinical complications [7]. Altogether, there are few cases in the literature describing siblings or a parent and a child having both elevated aPL levels and thrombotic manifestations. And even in these cases it is hard to conclude the exact role of aPL antibodies since there is either an autommune disease or some other hereditary prothrombotic feature involved as well.

There have been conducted statistical analyses on families with APS clusterings, and these have shown a possible autosomal dominant pattern of inheritance of aPL antibody production and associated clinical manifestations [8]. Still, no firm gene association has been identified for APS yet, in part because of the rarity of multiplex families to study and because of the possibility of another familial cause of thrombotic disease [9].

Other genetic analyses have shown certain HLA types linked to a higher frequency of positive aPL-antibodies. These are HLA-DR4, -DR7, -DRw53 and -DQB1*0302 , the same association pattern being found in patients with primary

APS and in those who are aPL positive connected with SLE or some other connective tissue disease.

Another representative antigen, β_2-glycoprotein-I (β_2-GPI), expresses a valine(247)/leucine polymorphism which could be another genetic risk for presenting anti-β_2-GPI antibodies and APS [10], [11].

Everything considered, mechanisms and pathophysiology of thrombosis in APS are highly heterogeneous and multifactorial, and that's why different genes and acquired factors seem to be involved [10], [7].

Conclusion :

Antiphospholipid syndrome usually presents with venous thromboses, especially deep venous thrombosis (DVT) of the lower extremities. APS presenting as arterial occclusion, especially one occuring at two sites at once is a very rare finding [11]. Additionally, familial clustering of primary APS is not common either. The genetic foundation of familial APS is a complex issue still being investigated and that's why this kind of reports are especially valuable in shedding light on it.

Conflict of interest: The authors declare that they have no conflict of interest.

References :

1. Berkun Y, Padeh S, Barash J, Uziel Y, Harel L, Mukamel M, Revel-Vilk S, Kenet G.(2006) Antiphospholipid syndrome and Recurrent Thrombosis in children. *Arthritis and Rheumatism* 55:850 – 855.

2. Miyakis S, Lockshin MD, Atsumi T et al. (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 4:295-306

3. Asherson RA, Cervera R, de Groot PG, et al.(2003) Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment. *Lupus* 12:530-4.

4. Avcin T, Cimaz R, Silverman ED, et al. (2008) Pediatric Antiphospholipid syndrome: Clinical and Immunologic Features of 121 Patients in an International Registry. *Pediatrics* Web site. http://www.pediatrics.org/cgi/content/full/peds.2008-1209v1 , Accessed April 26, 2011.

5. Méchinaud-Lacroix F, Jehan P, Debré MA, et al. (1992) Thrombotic manifestations and acute distal ischemia in primary antiphospholipid syndrome in children. *Arch Fr Pediatr*. 49:257-9

6. Evans RE, Dillon MJ, Alfaham M.et al. (1996) Antiphospholipid syndrome presenting as episodic limb ischaemia. *Archives of Disease in Childhood.* 75:342-343.

7. Namjou B. (2003) Antiphospholipid syndrome: genetic review. *Curr Rheumatol Rep*. 5:391-394.

8. Goel N,Ortel T. et al. (1999) Familial antiphospholipid antibody syndrome,Criteria for Disease and Evidence for Autosomal dominant inheritance. *Arthritis and rheumatism.* 2:318-327

9. Sestak AL, O'Neil KM. et al. (2007) Review: Familial lupus and antiphospholipid syndrome. *Lupus.* 16: 556—563.

10. Castro-Marrero J, Balada E, Vilardell-Tarrés M, et al.(2009) Genetic risk factors of thrombosis in the antiphospholipid syndrome. *Br J Haematol*. 147:289-96.

11. Provenzale, Ortel, Alen.et al. (1998) Systemic thrombosis in patients with antiphospholipid antibodies: Lesion Distribution and Radiologic findings. *American Journal of Roentgenology.* 170: 285.

Figure legends:

Fig. 1: Digital subtraction angiogram showing almost complete left popliteal artery occlusion measuring 5 cm in length. This figure depicts arterial patency prior to thrombolytic therapy.

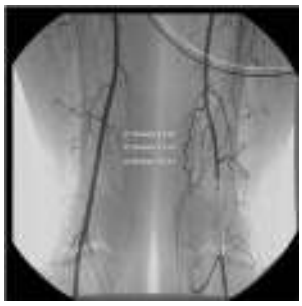

Fig. 2: Angiogram showing popliteal artery patency six hours after intravenous alteplase application.

Fig. 3: Angiogram showing a completely patent popliteal artery, 42 hours after succefully conducted thrombolytic therapy.