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CASE REPORT

Acute limb ischemia as presentation of pediatric antiphospholipid syndrome: case report

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune systemic disorder characterized by an increased risk of thrombosis and the presence of circulating antiphospholipid antibodies (aPL). A previously healthy 7-year-old girl was admitted complaining of right leg and foot pain with claudication. She had a malar rash, pallor and cooling of the limb, cyanosis of the toes and non-palpable popliteal and distal pulses. The vascular doppler showed a right popliteal artery occlusion and she started enoxaparin. Laboratory studies showed positive Coombs test, triple positive aPL, positive antinuclear and anti-double stranded DNA antibodies, C4 mild consumption. She started hydroxychloroquine, acetylsalicylic acid and warfarin, with posterior suspension of enoxaparin. Diagnosis of APS was confirmed 12 weeks later as aPL remained positive. There was a good clinical evolution with signs of re-vascularization. APS is rare in the pediatric population and has a wide clinical spectrum, becoming a diagnostic and therapeutic challenge due to the small number of pediatric studies.

Keywords: Antiphospholipid syndrome. Ischemia. Systemic lupus erythematosus. Thrombosis. Case report.

Isquemia aguda de membro como apresentação de síndrome antifosfolípide pediátrica: relato de caso

Resumo

A síndrome de anticorpos antifosfolipídos (SAAF) é uma doença autoimune multissistémica caracterizada por risco aumentado de eventos trombóticos na presença de anticorpos antifosfolípidos (aFL) persistentemente positivos. Criança de 7 anos, sexo feminino, previamente saudável, admitida por claudicação, dor e diminuição da temperatura do pé direito. Apresentava eritema malar, palidez e arrefecimento do pé, com cianose dos dedos, associados a ausência de pulsos poplíteo e distais. O ecodoppler demonstrou oclusão da artéria poplítea direita, pelo que iniciou enoxaparina em dose terapêutica. Destacava-se aFL triplo positivos; anticorpos anti-nucleares e anti DNA de dupla cadeia positivos; ligeiro consumo de C4; teste de Coombs direto positivo. Iniciou terapêutica com hidroxicloroquina, ácido acetilsalicílico e varfarina com suspensão da enoxaparina. Verificou-se boa evolução clínica, com evidência de revascularização da artéria poplítea. A SAAF é uma entidade rara em pediatria com um espectro clínico vasto, tornando-se um desafio diagnóstico e terapêutico pelo reduzido número de estudos pediátricos.

Palavras chave: Síndrome de anticorpos antifosfolípidos. Lúpus eritematoso sistémico. Trombose. Caso clínico.

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Keypoints

What is known

- APS is a rare immune-mediated systemic disorder classically manifested by thrombotic events.
- Pediatric APS might be underdiagnosed given theassociated absence of specific criteria for pediatric age.
- Arterial thrombosis is less frequent than venous thrombosis as APS presentation.

What is added

- Lower extremity arterial thrombosis is an APS presentation.
- Early diagnosis and treatment can reduce associated morbidity and mortality.
- Further studies are needed to improve the management and outcome of this disease.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune systemic disorder characterized by increased risk of arterial and/or venous thrombosis and maintained presence of circulating antiphospholipid antibodies (aPL), such as anti-cardiolipin (aCL) IgG and/or IgM antibodies, anti-β2-glycoprotein I (aβ2GPI) IgG and/or IgM antibodies, and lupus anticoagulant (LA)[1].

Formal APS classification requires the fulfilment of the updated Sapporo classification criteria: at least one clinical criterion (vascular thrombosis, pregnancy morbidity) and one laboratory criterion (presence of aPL on two or more occasions at least 12 weeks apart)[2]. However, pediatric APS is likely underdiagnosed because there are no validated criteria for pediatric age. Most individuals of pediatric age will not have the opportunity to meet pregnancy morbidity criteria and some non-criteria manifestations of APS, such as hematologic and neurologic, may be particularly common in children. Therefore, these are potential limitations of the adult-designed classification criteria.

Unlike adults, idiopathic thrombosis is quite rare in children. Children with APS do not usually have the commonly acquired risk factors for thrombosis, such as smoking, atherosclerosis or oral contraception. APS represents the most commonly acquired hypercoagulable state of immune-mediated etiology in children[3].

APS can be divided into two forms: primary or secondary. Primary APS is defined in the absence of an underlying disease, whereas secondary APS is observed in relation to other immune-mediated disorders, namely systemic lupus erythematosus (SLE).

We report a case of critical limb ischemia as the presentation of SLE-related APS in a female child.

Case report

A previously healthy 7-year-old girl was admitted to the emergency room complaining of right leg and foot pain with claudication worsening over three days. She had history of recurrent non-diagnosed cutaneous lesions and family history of SLE (father) and Psoriasis (mother and maternal grandfather). The remaining personal and family background were unremarkable. She reported a self-limited acute gastroenteritis in the previous week and denied previous trauma or medication intake. Fever, asthenia, anorexia, weight loss, red eye, arthralgia or oral ulcers were also denied.

Physical examination revealed a malar rash (Fig. 1), pallor and cooling of the limb below the knee (Fig. 2), cyanosis of the first and fifth toes and plantar region of the right foot (Fig. 3) and non-palpable popliteal and distal pulses. Nevertheless, there were no motor or sensitive deficits.

Laboratory studies showed prolonged partial activated thromboplastin time (60s/29s), positive direct Coombs test (IgG and C3d), triple positive aPL (LA, aCL IgG and IgM, and aβ2GPI IgG and IgM), positive antinuclear antibodies (ANAs) of 1/160 and anti-double stranded DNA antibodies (anti-dsDNA) of 45.5 UI/mL (positive if > 35 UI/mL) with mild consumption of C4 (11 mg/dL – reference range of 13-37 mg/dL) but normal C3 and CH50. Anti-extractable nuclear antigens screen was negative. The remaining thrombotic study (including protein S, protein C, antithrombin III, Factor V Leiden or prothrombin mutations, lipid profile, apolipoproteins, and homocysteine) was unremarkable. Nonthrombotic hematologic abnormalities were absent. Urinalysis and urine protein/creatinine ratio were normal.

From the imaging studies performed, a right popliteal artery occlusion was found on the vascular doppler of the lower limbs. Transthoracic echocardiogram showed no heart disease or intracardiac thrombi. Electrocardiography was also normal. Thoracic-abdominal-pelvic and inferior limbs computed tomography angiography corroborated the right popliteal artery occlusion, with a fully occlusive thrombus in a longitudinal extension of 3 cm, with partial downstream re-permeabilization with some filling defects in this segment (Fig. 4), but no changes in the remaining segments and no signs of signs of collateral arterial circulation.

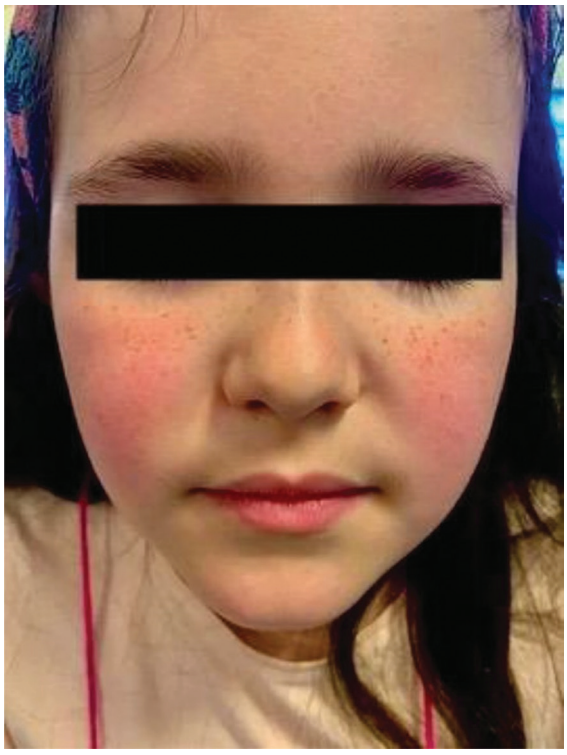

Figure 1. Malar rash.

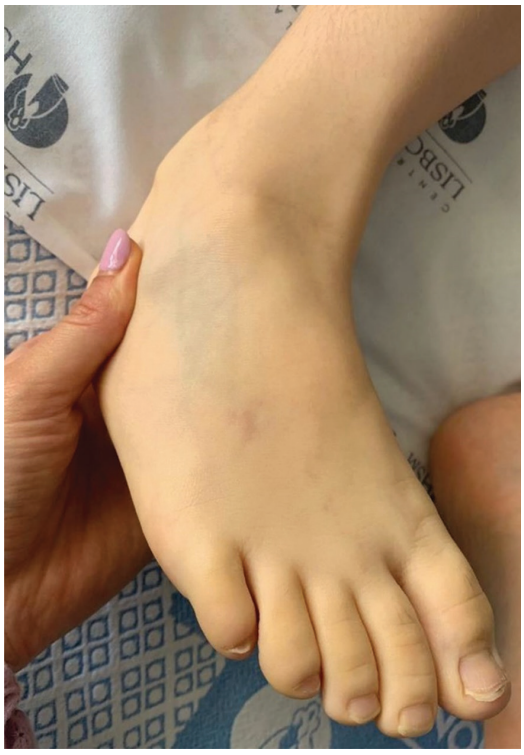

Figure 2. Pallor of the right limb and foot.

There was no evidence of inflammatory eye involvement on ophthalmological evaluation. She also had no affection of other organs and systems, namely renal, neurological, musculoskeletal or serosal.

Due to diagnosis of acute limb ischemia, she started anticoagulation treatment with subcutaneous low molecular weight heparin (LMWH), enoxaparin, 1 mg/kg/dose every 12h. After the diagnosis suspicion of APS, she started hydroxychloroquine, acetylsalicylic acid and warfarin, with posterior suspension of enoxaparin.

There was a good clinical evolution with resolution of pain and limp and signs of popliteal artery revascularization on Doppler. Diagnosis of APS was confirmed 12 weeks after the first laboratory tests as aPL remained positive.

At 6 months of follow-up, she remains asymptomatic, on anticoagulation treatment, followed regularly in both rheumatology and hematology clinics.

Discussion

APS is rare in the pediatric population and has a wide clinical spectrum, becoming a diagnostic and therapeutic challenge due to the small number of pediatric studies.

Primary and secondary APS occur in similar frequency in pediatric age[4]. SLE is the most common immune-mediated disorder associated with pediatric APS and is diagnosed at APS disease onset in 52-58% of the cases[4,5]. According to European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) new classification criteria for SLE, our patient met the criteria presenting with a EULAR/ACR score of 17 with positive ANAs higher than 1/80: one clinical (acute cutaneous lupus) and three immunological domains (presence of aPL and anti-dsDNA, and low C4). LA prolongs phospholipid dependent coagulation tests *in vitro*. Therefore, prolonged partial activated thromboplastin time can imply the presence of LA, which is a widely available test. Nevertheless, LA is associated with thrombosis rather than bleeding.

As in this case report, the occurrence of thrombotic events at the time of SLE diagnosis suggests that the inflammatory state of active SLE may play an important role in increasing the risk of aPL-related thrombosis.

Arterial thrombosis is less frequent (32-35%) than venous thrombosis (60-65%) as APS thrombotic presentation[4,6]. The most common manifestation of arterial thrombosis is cerebral ischemic stroke. Lower

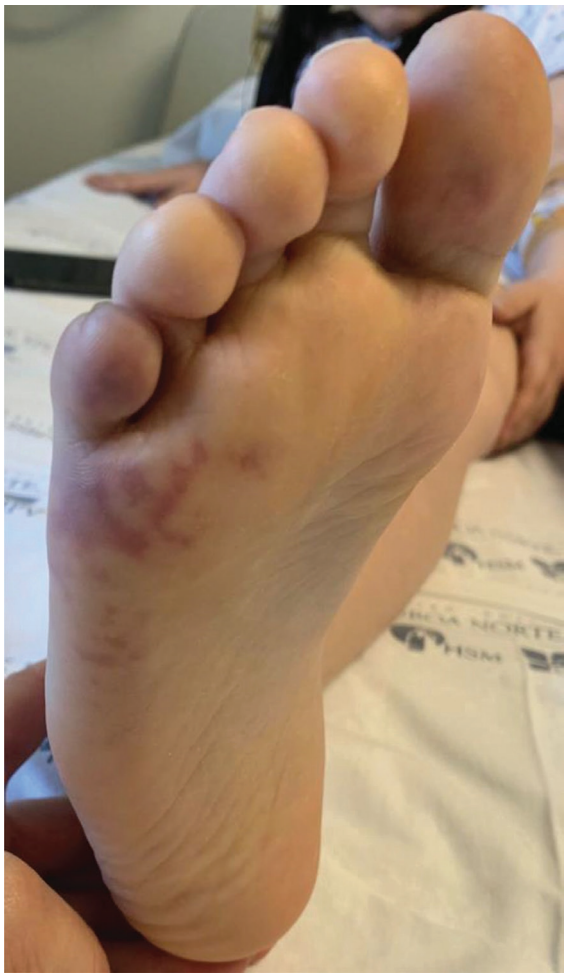

Figure 3. Cyanosis of the first and fifth toes and plantar region of the right foot.

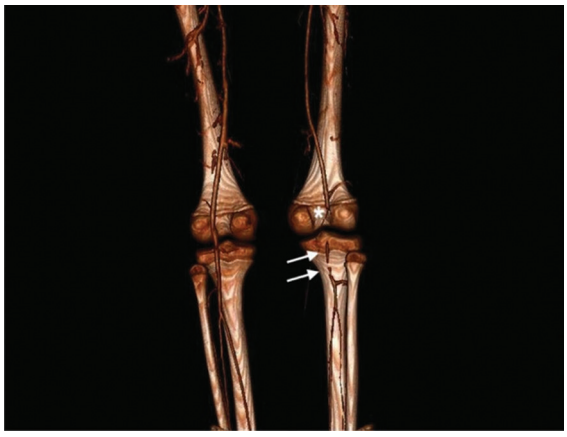

Figure 4. Inferior limbs computed tomography angiography showing the right popliteal artery occlusion (*), with partial downstream re-permeabilization with some filling defects (arrows).

extremity arterial thrombosis is even rarer, representing about 2% of thrombotic events[4].

Other non-thrombotic APS manifestations, noninclued in the classification criteria, are Evans syndrome, thrombocytopenia, leukopenia/lymphopenia, autoimmune hemolytic anemia, livedo reticularis, Raynaud phenomena, migraine headaches and chorea, among others.

Inherited prothrombotic disorders are frequently associated with APS, however, our patient´s thrombotic study was normal. Besides the immune-mediated disease, there were no additional acquired prothrombotic risk factors identified in our patient, such as immobilization or concurrent infectious disease. She had only a self-limited acute gastroenteritis in the previous week of disease onset.

Unfortunately, data on the incidence, risk of thrombosis and effective treatment of pediatric APS are scarce and heterogeneous. Pediatric patients with APS seem to have a high risk of recurrent thrombotic events (19-59%), usually occurring in similar blood vessel type[4-6]. Yet the duration and degree of antiplatelet and anticoagulants to prevent recurrence remains unclear. There is no difference in initial acute treatment of APS-related thrombosis compared to other causes of thrombosis, consisting of anticoagulation either with LMWH or unfractionated heparin. For long-term anticoagulation, heparin is usually switched to a vitamin K antagonist such as warfarin, as direct oral anticoagulants are not well studied. INR goal is also controversial, but a range between 2-3 is frequently used[1]. Most authors advocate lifelong anticoagulation with warfarin for secondary prevention of thrombosis in secondary APS pediatric patients, as there is continuous risk of recurrence due to ongoing endothelial perturbation[1,7,8]. In arterial thrombosis, adding anti-aggregation therapy with low-dose aspirin is commonly recommended. Hydroxychloroquine seems to lower the risk of both venous and arterial thrombosis in SLE patients. Therefore, our patient started aspirin and hydroxychloroquine, in addition to anticoagulation, after suspicion of SLE-related APS. More multicentric collaborative studies will be needed to better understand the clinical course of pediatric APS and, hence, its adequate treatment.

This article reports an unusual presentation of childhood-onset SLE-related APS. Thereby, we aim to warn about acute limb ischemia as a possible presentation of APS, in this case secondary to SLE, as early diagnosis and treatment can reduce associated morbidity and mortality.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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