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Experience with multiple stent implantations in primary antiphospholipid syndrome in childhood: a case report

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ABSTRACT

The antiphospholipid syndrome (APS) is an autoimmune condition characterized by the persisting presence of antiphospholipid antibodies in association with thrombosis and/or pregnancy morbidity. Primary APS is quite rare in childhood and exact prevalence is not known. However, substantial proportion of thrombotic events in children is being attributed to APS. We herein present a 9-year-old boy presented with impending pericardial tamponade and large pleural effusions likely secondary to transudation of fluid from his gradually developed collateral circulation which was resulted from almost completely occluded vena caval system due to primary APS. He was treated with multiple angioplasty-stenting which offered symptomatic relief and better quality of life. To our knowledge, this is the first reported paediatric case of primary APS presented with extensive occlusive lesions in both caval systems and treated with repeated endovascular stent placements.

Introduction

The antiphospholipid syndrome (APS) is a multisystem autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity in association with antiphospholipid antibodies (aPL). This syndrome can either be primary or secondary to other autoimmune diseases, such as systemic lupus erythematosus (SLE) (1-3). Disease onset before age 15 has been reported in only 2.8% of the patients (4). The frequency of aPL-related thrombotic events is low in paediatric population. However, a recent study demonstrated that deep vein thrombosis has been the most common initial manifestation in children with APS and comparable to adult patients (4,5). In the same series, recurrent thromboses were observed in a third of patients (5). Long-term anticoagulation is needed in patients who experience an aPL-related thrombosis due to the risk of recurrence (6). However there is no consensus concerning the duration and intensity of this therapy (7). There are few anecdotal reports in using combinations of thrombolytic therapies, transluminal angioplasty and stent implantations as primary or salvage therapies in adults (8, 9). To our knowledge, there is no publication about stent implantations in paediatric primary APS to date.

We herein present the case of a 9-year-old boy with primary APS who experienced recurrent thrombotic events treated by angioplasty-stenting of both inferior and superior vena cava.

Case report

A 9-year-old male was admitted to Childrens Hospital Los Angeles for a three-year history of intermittent body swelling, which was attributed to allergies and had been treated with furosemide and antihistamines. On admission he had moderate respiratory distress, his temperature was 37.6°C, heart rate 142/minute, respiratory rate 24/minute, blood pressure 101/87 mmHg. He had facial swelling and a full neck with distended veins, moderate abdominopelvic swelling and multiple extended superficial veins on the chest and abdomen. He had distant heart sounds and his left lung field had decreased breath sounds. The abdomen was soft with a liver edge 10 cm below the right costal margin and a tender spleen tip palpable 3 cm below the left costal margin. He had mild scrotal swelling. Extremities were warm with symmetric upper and lower pulses, no cyanosis and 1+ pedal edema bilaterally. Neurologic exam was unremarkable. A complete blood count revealed a white blood cell count of 7800/mm^3, a hemoglobin of 12.4 g/dL, and platelets of 394,000/mm^3. Urinalysis, renal and hepatic functions were normal. Erythrocyte sedimentation rate was 30 mm/hr. He had mildly elevated prothrombin (15.4 sec) and partial thromboplastin times (46 sec). Chest x-ray demonstrated a large opacification of the left base, and a widened mediastinum. Computed tomograms (CT) of chest showed large left-sided and smaller right-sided pleural effusions and a large pericardial effusion. The CT scans also showed a markedly dilated azygous and intercostal veins. Echocardiogram confirmed a large pericardial effusion with impending tamponade. The patient was placed both a pericardial drain and a leftsided

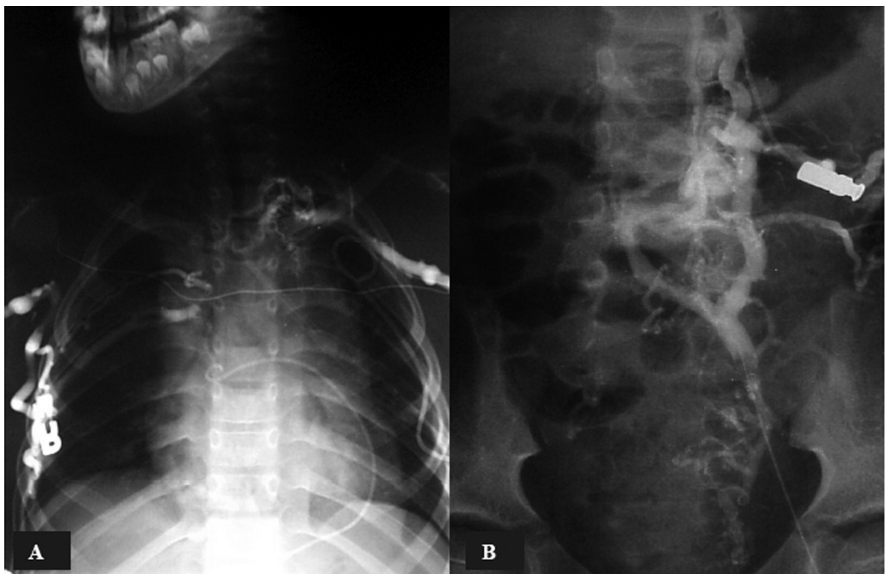

Fig. 1A. Bilateral upper extremity venograms showing obstruction of both subclavian veins and the superior vena cava as well as large collateral intercostals and long thoracic veins. **B.** Lower extremity venogram showing obstruction of the inferior vena cava and the recannulation of an embryonic vessel as well as other collaterals.

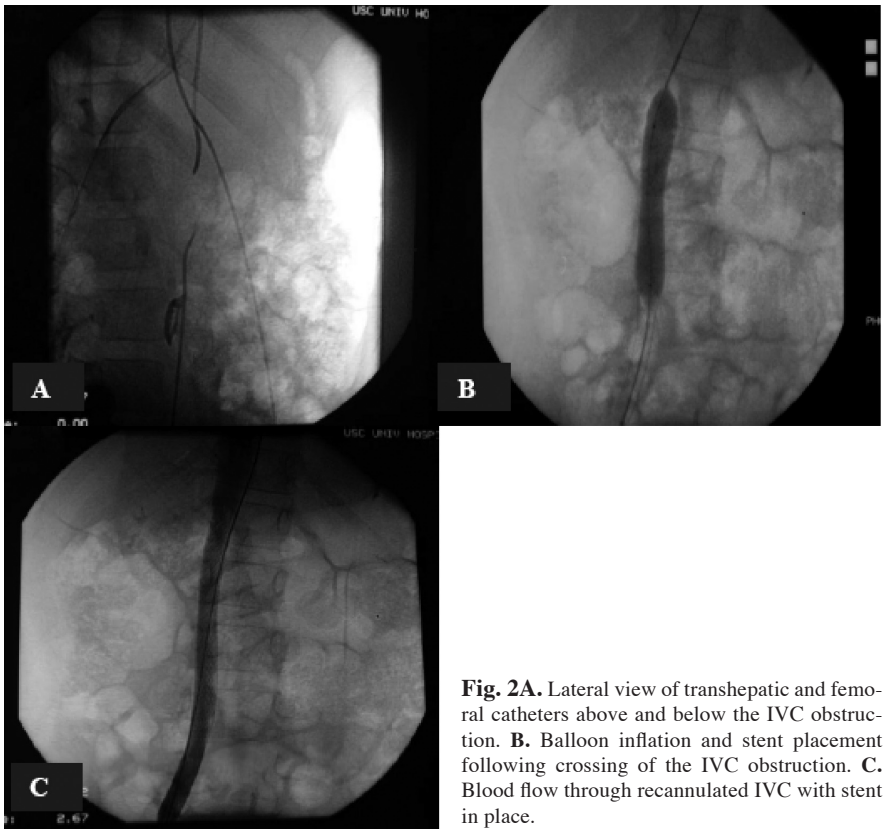

Fig. 2A. Lateral view of transhepatic and femoral catheters above and below the IVC obstruction. **B.** Balloon inflation and stent placement following crossing of the IVC obstruction. **C.** Blood flow through recannulated IVC with stent in place.

chest tube. Two hundred milliliters of fluid was drained from the pericardium and 615 milliliters of fluid was removed from the chest cavity. Analysis of fluids revealed exudative pericardial and transudative pleural fluid. Cultures were negative as were cytology analyses for malignant cells. Given the aberrant vasculature in the CT images, venography was performed, which demonstrated thrombosis and complete obstruction of the superior vena cava (SVC) with extensive venous collaterals, including the intercostal and pericardial veins. Lower extremity images showed obliteration of the inferior vena cava (IVC) at the level of the liver with similar collateral vascularization (Figs. 1 A, B). Protein C and S levels and activities were normal, as were antithrombin III levels. Factor V Leiden mutation was negative, as was DIC panel. Antinuclear, antidouble stranded DNA, anti-Smith and anti-ribonucleoprotein antibodies were negative. Complement levels were normal. Lupus anticoagulant (LA) was positive (by LA sensitive aPTT and the dilute Russell's viper venom time) and an extended aPL panel revealed antiphosphatidic acid Ig M antibodies (by ELISA) twelve weeks apart.

The patient was started on low molecular weight heparin (LMWH) with a dose of 100U/kg subcutaneously two times a day and azathioprine 2 mg/kg with the diagnosis of APS. Anti-factor Xa levels were monitored regularly in order to titrate his heparin dose. The patient did well on this treatment and his pericardial drain and chest tube were discontinued. He was eventually discharged on LMWH, furosemide and azathioprine. Due to the extent and the severity of his venous occlusions the patient was referred to an interventional radiologist. Two months after his initial presentation, he underwent a successful stent placement in his IVC (Figs. 2A, B, C). He had near complete resolution of his edema for almost 2 years. However, during his follow up visits, 6 months after the initial presentation, he was found to have a persistently positive lupus anticoagulant, while anti-phosphatidic acid antibodies normalized. After one year azathioprine were discontinued. At that time lupus anticoagulant was also negative. After two years he developed acute, painless swelling of his left lower extremity. A repeat evaluation showed a recurrence of his aPL antibodies in the form of positive IgM phosphatidylserine antibodies. His only medication at that time was prophylactic LMWH with a dose of 50 U/kg daily. A repeat venogram showed stenosis of his IVC distal to his initial stent. He underwent a second procedure of balloon dilation and stent replacement with resolution of the obstructive symptoms. Six months

later the patient again developed painless leg swelling and a repeat venogram showed a restenosis of the stent. He underwent a third balloon dilation which resulted in partial resolution of the edema. He continued to have intermittent upper and lower extremity swelling and finally a SVC stent was placed approximately 3 three years after the initial IVC stent. Even though he experienced transient improvement he continues to have persistent edema, mainly in his lower extremities and scrotal area ever since. He underwent several more balloon dilatations and had a lymphatic shunt placed without significant clinical benefit. He is currently on warfarin with a dose of 0.2 mg/kg (for International normalized ratio between 2-3). The family is considering the recommendation of bypass surgery with replacement of obstructed vessels with a surgical graft.

Discussion

Antiphospholipid syndrome is the leading cause of thromboembolic diseases in children (10). A recent paediatric multicenter study demonstrated that 82% of patients with APS primarily presented with vascular thrombosis (arterial 39%, venous 43%). A third of these patients experienced recurrent thrombotic events, which occurred mainly in patients who did not receive sufficient anticoagulation. After a follow-up of 5.7±4.8 years, 16 of 27 children had CNS symptoms, 9 developed hematologic disorders, and 5 (all females) had developed SLE (5). We were unable to detect any precipitating event in our patient's history and no evidence of an associated autoimmune process such as SLE in the long-term follow-up. Our patient presented rather acutely with impending pericardial tamponade and large pleural effusions secondary to transudation of fluid from his venous system caused by the high pressure in his dilated collateral vessels. This was likely due to the decompensation of the venous occlusion that had probably developed several months if not years earlier. Such a massive obstruction of the upper and lower caval system has not been previously described in a child.

Anticoagulation with heparin followed by oral anticoagulation is the standard treatment for an acute venous or arterial thrombosis. Due to the lack of clinical evidence the duration and intensity of anticoagulation in children with APS are debatable. An intermediate intensity anticoagulation treatment with a target INR of 2.0-2.5 has been suggested (11, 12). It is also recommended that the target INR in those patients with recurrent events on warfarin therapy and/or arterial events should be between 3-4 (13). However for those patients that fail to respond to traditional anticoagulation, interventional radiological or surgical treatments have to be considered. A recent report in adult patients found that stent placements in SVC syndrome were effective in the short term, and did not, despite frequent need for repeat interventions, adversely affect future surgical reconstruction (14). Despite effective oral anticoagulation, our patient developed recurrent stent thromboses which required repeat balloon dilation and stent replacements. Each of those interventions provided him a prompt but transient relief of his symptoms and an improved quality of life. He is currently being evaluated for bypass surgery. To our knowledge our case is the first child who has undergone endovascular stent placement on multiple occasions due to recurrent venous thromboses resulting from primary APS. Successful arterial and venous angioplastic interventions and stent implantations have been reported in adults with APS (8, 9). Endovascular interventions for both venous and arterial occlusions are increasingly being recognized in the paediatric population due to improved technology and treatment strategies for previously lethal childhood diseases such as malignancies, congenital heart diseases, liver failure and various other diseases (15-17). Since, acute and recurrent stent thrombosis in coronary events were reported in adults with primary APS (18, 19), endovascular stenting should be performed in selected individuals.

In conclusion our case is of remarkable interest for several reasons. To the best of our knowledge this is the first reported paediatric case of primary APS with almost complete occlusion of both caval systems refractory to oral anticoagulation. Additionally, this is the first published case in the paediatric literature that demonstrates the potential benefit of interventional stent implantation on an APS background. Even though this procedure only offered transient symptom relief in our patient, it may be a reasonable treatment alternative to vascular surgery in selected patients with extensive APS syndrome who failed other treatments.

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