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Catastrophic Anti-phospholipid Syndrome Presenting with Symmetrical Peripheral Gangrene

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Authors' contributions

This work was carried out in collaboration among all authors. Author UZ designed the concept, acquisition, analysis and interpretation of data. Author AF drafted and critical revision of the article. Author ZZ approved the final version. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Introduction: Anti-phospholipid syndrome (APS) is an acquired auto-immune thrombophilia and is very rare in children presenting with skin manifestations.
Case Report: A case of 12 years old female who presented to the Emergency with discoloration of arms and legs and later developed gangrene which then auto-amputated. Anti-cardiolipin antibodies were found to be positive and skin biopsy findings were consistent with APS. She was diagnosed with catastrophic anti-phospholipid syndrome. Anti- ds antibodies were found to be negative.
Conclusion: Criteria for diagnosing APS in children should be developed as the adult APS diagnostic criteria doesn't seem to apply on peadiatric patients. Prior studies too apply emphasis on this fact.

Keywords: Anti-phospholipid syndrome; cardiolipin antibodies; gangrene; auto-amputation.

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ABBREVIATIONS

CAPS= catastrophic anti-phospholipid syndrome; ANA= anti-nuclear antibody; AMA= anit-mitochondrial antibody; AGPCA= anti-gastric parietal cell antibody; c-ANCA= cytoplasmic anti-nuclear antibody; p-ANCA= pericytoplasmic antinuclear antibody; anti-ds DNA= anti-double stranded DNA; ASMA= anti-smooth muscle antibody.

1. INTRODUCTION

Anti-phospholipid syndrome (APS) is an acquired auto-immune thrombophilia. It can be primary or secondary [1]. It can be associated with other auto-immune conditions in which case it is known as secondary APS otherwise it is known as primary APS when presenting with isolated APS features. Most common auto-immnue disorder associated with APS is SLE. If it is not present at the time of diagnosis there is a high probability of the patient developing it later in life [2]. In young children, it is more common to found primary APS as compared to secondary APS. Clinical manifestations of this syndrome are heterogenous. It is more common in adult females presenting with recurrent miscarriages and is very rare in children [3]. Even the largest APS cohort study reports APS onset in children aged less than 15 years in only 2.8% of population [4].

The adult diagnostic criteria for APS revised in 2006 include one laboratory and one clinical criterion for confirmed diagnosis (as shown in Table 1). Recently, adult diagnostic criteria is used for diagnosis of APS in children however some studies suggest that there should be separate diagnostic criteria for children aged less than 15 years of age because some children do not match this criteria [5].

Rarely APS presents with skin manifestations. Skin lesions seen in APS are mostly manifestation of another variant of APS known as catastrophic anti-phospholipid syndrome (CAPS) which is characterized by multi-organ involvement along with microvasular occlusions. The diagnostic criteria for CAPS is given in Table 2. Some skin lesions associated with CAPS include livedo reticularis, acrocyanosis, large cutaneous necrosis, palmar erythema, digital

Table 1. Diagnostic criteria for anti-phospholipid anti-body syndrome [16]

Clinical criteria	Laboratory criteria
1. One or more episodes of arterial, venous or small vessel thrombosis 2. After 10th week of gestation unexplained deaths of one or more morphologically normal fetus , pre-term births of normal neonate before 34th week of gestation because of maternal complications such as eclampsia, or severe pre-eclampsia or placental insufficiency, 3 or more unexplained consecutive miscarriages prior to 10th week of gestation with maternal abnormalities excluding any maternal or paternal chromosomal abnormalities.	1. Lupus anticoagulant (LA) present in plasma on one or more occasions with minimum 12 weeks interval in between. 2. Anti-cardiolipin IgM or IgG present in medium or high titers i.e greater than 40GPL/MPL units or greater than 99th percentile on two or more occasions with minimum interval of 12 weeks in between. 3. Positive titers of Anti-b2–glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma greater than 99th percentile on two or more occasions with minimum interval of 12 weeks in between.
APS is diagnosed in the presence of one clinical and one laboratory criteria.	

Table 2. Diagnostic criteria for catastrophic anti-phospholipid anti-body syndrome [17]

1. *Syndrome involving three or more organs, tissues or systems.* 2. *Development of clinical manifestations in less than a week* 3. *Histopathological confirmation of small vessel occlusion, vasculitis may co-exist.* 4. *Laboratory investigations demonstrating positive anti-phospholipid antibodies 12 weeks apart.*
The condition is said to **Definite Catastrophic Anti-phospholipid Syndrome** if all four criteria are met. The condition is said to be **Probable Catastrophic Anti-phospholipid Syndrome** if: *a. Instead of three, two organs/tissues/systems are involved.* *b. Absence of anti-phospholipid antibodies* c. *Development of small vessel occlusion after a month, despite anti-coagulation*

gangrene and ischemic ulcers [6]. Few studies report gangrene associated with anti-phospholipid syndrome however this presentation is very rare [7]. More commonly gangrene in anti-phospholipid syndrome is associated with SLE [8].

2. CASE HISTORY

12 years old female patient with no-comorbids presented to the Emergency room in critically ill condition with swelling and discoloration of upper and lower limbs. She previously had episode of loose motions and vomiting for which she was was treated in her locality after which she developed blackish discoloration of upper and lower limbs. On examination her respiratory rate was 35 breaths/min, pulse 150 bpm, temperature 38 degree centigrade, blood pressure 100/60 mm of Hg. She had no previous history of such episode. She denies history of any drug intake, breathlessness or hemoptysis. Upper and lower limb pulses were not palpable. Rest of the systemic examination was unremarkable.

Fig. 1. Upper limbs showing gangrene

Investigations revealed Hb 4.8 gm/dL, platelet count 42×10^9, neutrophils 63%, lymphocytes 33%, eosinophils 2%, basophils 2%, Urea 116 mg/dL, Creatinine 3.5 mg/dL, calcium 5.1 mg/dL, sodium 138 mg/dL, Potassium 3.2 mg/dL, chloride 105 mg/dL, magnesium 1.06 mg/dL, albumin 2.8, raised CRP (24 mg/L). Urine DR showed positive leukocyte esterase (>25 Leuc/uL), protein traces and occult blood. Total bilirubin was 7.6, direct bilirubin 3.2, ALT 165 u/litre, ALP 249 u/litre. Direct and indirect Coombs test were negative. PT was 13.7 seconds (control 11.4), aPTT was 27.4 seconds (control 26.6 seconds). ANA, AMA, ASMA, AGPCA, c-ANCA, p-ANCA, anti-ds DNA were negative. Anti-cardiolipin IgG was positive (24.1), cardiolipin IgM was also positive (13.1).

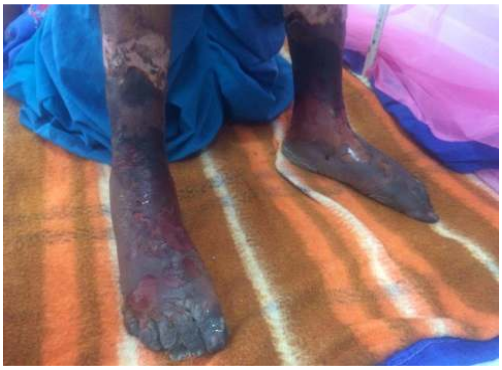

Fig. 2. Lower limbs showing gangrene

Ultrasound of arms and legs revealed no flow below cubital fossa and popliteal fossa respectively. Discoloration of arms developed into symmetrical gangrene in both upper and lower limbs below the elbow and knee joint respectively as shown in figures. Overtime gangrenous parts got auto-amputated. Skin biopsy reports were consistent with findings of anti-phospholipid syndrome. Echocardiograph was normal (Ejection fraction 60%, normal sized atria and ventricles and no valvular abnormalities.

Informed consent was taken from patient to report her condition as well as pictures prior to submission.

3. DISCUSSION

CAPS can involve multiple organ systems. Dermatological manifestations may be the first one to appear. Thrombotic manifestations may follow on. They can either be superficial venous thrombosis or deep vein thrombosis or even arterial thrombosis. One study reports 28 children with APS, venous thrombosis in 12 patients, arterial thrombosis in 11 patients and non-thrombotic manifestations in 5 patients [9]. Thrombosis of deep limb veins along with pulmonary embolism is one of the most common manifestations of APS. Ischemic stroke can also manifest along with myocardial infarction, peripheral gangrene, and occlusion of any main circulations such as mesenteric, portal, intracranial and retinal [10]. Non-classical clinical manifestations of APS include thrombocytopenia, hemolytic anemia, chorea, transverse myelitis,

epilepsy, heart valve disease. Most common of these non-classical manifestations were hematologic manifestations [11].

Presentation of APS sometimes clinically mimics Beurger's disease which is a thromo-inflammatory disease of medium sized arteries and veins and in later course may lead to auto-amputation [12]. We suspected Beurger's in our patient but the diagnosis was excluded on negative ANCA as well as no history of active or passive smoking.

Diagnosis of APS is challenging as it lacks a gold standard investigation. Lupus anti-coagulant would have been a big help in diagnosis but couldn't be done due to financial constraints Infection was found as a trigger for development of clinical manifestations which is similar to other studies held in past [13,14]. Patient was started on methylprednisone, cyclophosphamide and later methotrexate along with broad spectrum antibiotics such as meroneum and vancomycin. Treatment in APS in patient's based. There is no modality of treatment currently developed to manage syndromes of APS. However improvements have been seen with anti-coagulation, plasma exchange, high dose corticosteroids with or without Immunoglobulins [15]. Currently there is no evidence of SLE in this patient however this patient is at high risk of development of SLE later in life. There is much need of further research regarding diagnosis of APS in peadiatrics.

4. CONCLUSION

This is an interesting presentation of probable CAPS in female child with symmetrical peripheral gangrene. CAPS is found in less than 1% of patients with APS. This form of APS is associated with very high morbidity and mortality. Bad prognosis associated with CAPS is due to involvement of multiple organs along with hematological manifestations. The clinical features are found to be overlapping with other thrombotic diseases therefore it is suggested that treatment should be started even before the confirmation of diagnosis to prevent catastrophic events.

Lastly, there is immense need of developing diagnostic criteria for peadiatric patients with APS. Because peadiatric manifestations are different than adult manifestations of APS. Cardiolipin antibody titers in or patient were lower than adult APS diagnostic criteria suggests, but still the patient was diagnosed of CAPS.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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