Abstract
This report describes a rare case of Juvenile Systemic Lupus Erythematosus (JSLE). A young 13-year-old girl presented to the Civil Hospital Karachi on February 15, 2019 with gangrene as the only manifestation of this autoimmune disease. JSLE has several clinical manifestations such as butterfly rash, fever, joint pain, cardiac problems like pericardial infusion and neuropsychiatric disorders. However, in this case gangrene was the only presenting symptom; only laboratory investigations — anti-SSA and anti-ribosomal P protein — were suggestive of JSLE, while anti dsDNA, considered to be the most sensitive and reliable diagnostic tool for Systemic Lupus Erythematosus (SLE), was negative. Raynaud's phenomenon and gangrene have been described as rare symptoms, with gangrene occurring in only a small percentage of SLE patients. Moreover, the patient had received a blood transfusion a few months ago in Hyderabad which was suspected to be the cause of the transmission of infection which lead to polyclonal activation of lymphocytes.

Keywords: Juvenile Systemic Lupus Erythematosus, Gangrene, Auto-immune, Vasculitis.

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Introduction
Juvenile onset systemic lupus erythematosus (JSLE) is a systemic inflammatory disorder which manifests before the age of 16 in 10-20% of all SLE cases.\textsuperscript{1}

It is extremely rare with an annual global incidence of 0.36-2.5 cases per 100,000 children, with the disease being more common in girls and young women (4.7-5.6:1), though the female predominance is less marked in children as compared to adults.\textsuperscript{2}

Studies suggest that the disease phenotype in JSLE is significantly more severe as compared to SLE in adults.\textsuperscript{3} It involves variable clinical presentations which make its diagnosis challenging as compared to adult-onset SLE. Major organ involvement includes lupus nephritis, haematological dysfunction (as anaemia, thrombocytopenia and lymphopenia), neuropsychiatric involvement, joint and skin involvement and fever as the most common presenting features of this disease.\textsuperscript{2}

While lymphadenopathy and hepatosplenomegaly were slightly rarer manifestations of the disease, digital gangrene along with panniculitis and autoimmune haemolytic anaemia were the rarest and were each observed in only a single patient participating in one study.\textsuperscript{4} The multitude of symptoms exhibited in SLE due to multi-system involvement vary, as they are influenced by factors including ethnicity, climate and country. Studies have been conducted on Pakistani patients belonging to Sindh, Punjab and Khyber Pakhtunkhwa provinces, investigating the initial clinical manifestation of SLE. While there are differences in the initial clinical presentation of SLE patients based on their geography, all studies reported constitutional symptoms (fever, fatigue and joint aches) as the most common finding. Renal involvement as lupus nephritis was found in a significant number of patients from Sindh and Punjab,\textsuperscript{5,6} while mucocutaneous findings as malar rash, mucosal ulcers and Raynaud’s phenomenon were common in patients of all three provinces. Vasculitic infarcts were more common in the cohort belonging to Sindh (17%) than that of Punjab (4.9%). Peripheral gangrene was not reported in any of these studies.\textsuperscript{5-7}

Case Report
A 13-year-old girl presented to the Internal Medicine (IM) department at Civil Hospital Karachi (CHK) on February 15, 2019.

Her medical history revealed that she had initially sought treatment at Benazir Bhutto Trauma Centre, Karachi. Her Doppler Ultrasound Study suggested peripheral gangrene to be the only significant finding and, consequently, she was clinically diagnosed to have thrombosis based on her thrombophilia profile which revealed elevated levels of Factor V Leiden and anti-
thrombin III with normal protein S and C levels. This was followed by the confirmation of autoimmune disease based on a positive Anti-nuclear Antibodies (ANA) test. She had been prescribed Deltacortril, Clexane and Warfarin to manage the disease conservatively. Moreover, according to the patient’s attendant, the patient also underwent a blood transfusion at Hyderabad, three to four months before her hospitalisation at CHK, to compensate for nutritional deficiency.

At the IM department of CHK, she presented with complaint of blackish discoloration of both feet since the past two months. She had no other presenting symptoms nor any known comorbidities. Physical examination of her left foot revealed a blackish discoloration involving all five toes, extending up to the dorsum. Sensory system of the foot was severely impaired, with dorsalis pedis and posterior tibial pulses not being palpable. The right foot showed a similar black-purplish discolouration limited only to the first, fourth and fifth toes. General articular sensations in this foot were intact, and the dorsalis pedis and posterior tibial pulses were palpable.

On admission, the patient’s precardium, chest and central nervous system examinations were unremarkable. She had orientation of time, place and person. The patient was afebrile with a pulse rate of 90 beats per minute (BPM), a respiratory rate of 21 per minute with an oxygen saturation of 96%.

The patient was asked to have abdominal ultrasound and bilateral lower limb Computed Tomography (CT) angiography done for further diagnoses. Her abdominal ultrasound was normal, while CT angiography suggested thrombosis of bilateral distal popliteal arteries with attenuation of distal anterior tibial and peroneal arteries.

The complete blood count (CBC) showed haemoglobin (Hb) of 12.4 g/dL (normal = 12.0-15.5 g/dl) and a total leukocyte count (TLC) of 13.04x10^9/L (normal = 4.5-11.0x10^9/L), with neutrophils being 59% (normal = 40-60%) and lymphocytes 33% (normal = 20-40%). The mean corpuscular volume (MCV) of 81.9 femtolitres (fl/cell) (normal = 80-96 fl/cell) with a hematocrit of 26.7% (normal=36-48%) and platelets of 312 x 103 per cubic millimetres (normal=150,000-450,000 / mm3) was noted. The basic metabolic panel indicated normal sodium, potassium, calcium, magnesium and chloride levels. Blood urea nitrogen (BUN) and creatinine were also within normal limits. Her urine D/R was normal except for a slightly elevated count of red blood cells.
ranging 4-6 high power field (hpf) (normal<4). Furthermore, her C-reactive protein and Lactate Dehydrogenase test indicated no abnormality.

Her nutritional profile was deranged showing serum iron at 36 microgram per decilitre (μg/dL) (normal=60-140 μg/dL) with a transferrin saturation at 11.1% (normal>16%). Vitamin B12 at 163.7 nano grams per millilitre (ng/mL) (normal=200-900 ng/mL) and folic acid at 18.0 nano grams per millilitre (ng/mL) (normal=2.7-17.0 ng/mL) was observed.

Her extractable nuclear antigen (ENA) profile displayed the presence of Ribosomal-P protein and Sjögren’s-syndrome-related antigen A (SSA/Ro) auto-antibodies. It showed the absence of anti-double stranded DNA (anti-dsDNA), Anti-neutrophil cytoplasmic (aNCA) and proliferating cell nuclear antigen (pCNA) anti-bodies with normal cryoglobulin and homocysteine levels. Her lupus anti-coagulant was also observed to be normal.

Her complete ENA profile along with her bilateral lower limb CT angiography enabled us to reach a final diagnosis of necrotizing vasculitis secondary to JSLE. A multidisciplinary team was set up, which decided that conservative treatment was best in this case. She was started on immunosuppressive drugs including Solumedrol, Deltacortril and Azathioprine, antithrombotic drugs including Enoxaparin and Warfarin, along with Piperacillin and Tanzobactam to prevent bacterial body infections and HCQ. Her nutritional profile was managed by prescribing Calcium carbonate and Folic Acid. Her first follow up on March 19, 2019 was uneventful.

The patient was readmitted on March 26, 2019 as her left foot was painful, more swollen and pus was discharging from the necrotic ulcers (Figure-2a). Physical examination of her left foot revealed visible signs of auto-amputation. After consultation with orthopaedics, the patient underwent surgery to remove the necrotized tissue. The patient was subsequently discharged and prescribed a regimen of Cefspan, Clexane, Deltacortril, Adalat, HCQ and Zantac. She was further advised to follow-up with a complete lab workup, including ENA, antiphospholipid antibodies and anti-dsDNA to monitor prognosis. Her follow-up visit was unremarkable with positive anti-dsDNA and an ENA profile positive for anti SSA/Ro antibodies. She was also strongly positive for lupus anti-coagulant of 105.8s as well as anti cardiolipin (aCL) IgG and aCL IgM antibodies. ANA profile displayed nucleolar pattern. Based on the presence of lupus anti-coagulant and IgG and IgM aCL on her follow-up after amputation, it was suspected that she was suffering from anti-phospholipid syndrome (APS) along with SLE. She was advised a test for phospholipid antibodies to confirm its presence and was referred to the rheumatology clinic at Jinnah Postgraduate Medical Centre (JPMC) instead of CHK for any subsequent follow-ups.

**Discussion**

JSLE has a number of clinical manifestations including myocardial infarction, pleural effusions, ascites, arthralgia, malar rash, fever, pleuritic chest pain and a positive ANA, making diagnosis easy. The patient described above presented with only gangrene of the distal feet and no other dermatological, cardio-pulmonary or abdominal irregularities. This presentation led to an initial diagnosis of arterial insufficiency due to peripheral artery disease, which was ruled out by a Doppler ultrasound study. In such cases, ANA is used to determine auto-immune involvement and diagnosis is reached at, based on the patient’s ENA profile, following a positive ANA result.
Prevalence of double-stranded DNA autoantibodies is much higher (70%) in SLE than other autoimmune diseases, making it a highly sensitive diagnostic tool. The patient tested negative for the aforementioned test, complicating her diagnosis. In 25-30% ANA positive SLE patients, autoantibodies against Ribosomal-P protein and SSA may be present. This may prove instrumental in diagnosing SLE, should the anti-dsDNA results return negative.

Although dermatological manifestations of SLE such as malar rash, oral ulcer, photosensitivity, alopecia, and discoid lupus erythematosus are common, gangrene remains an extremely rare symptom manifesting in only 1% of patients. Gangrene in children has been described in previous reports, but very rarely as the only presenting symptom.

Vasculitis is a principal pathological characteristic of several connective tissue diseases, including SLE. In a study by Barile-Fabris et al, incidence of cutaneous vasculitis in SLE ranged between 19% and 28%, and its clinical manifestations ranged from palpable purpura and petechiae, papulonodular lesions, livedo reticularis, cutaneous infarction, erythema with necrosis to superficial ulcerations.

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Lupus vasculopathy can be of inflammatory or thrombotic origin. Immune-mediated complex lesion in the blood vessel wall plays a potent role in the pathogenesis of vascular involvement in SLE. This involves immune-mediated activation of endothelial cells with expression of adhesion molecules which then bind proteins to the vessel wall. A typical vasculitis involves inflammation of the vessel wall and ischaemia leading to necrosis while a thrombus in the lumen of the affected artery occurs less often.

A study by Bengtsson et al to evaluate the risk factors associated with SLE showed that blood transfusions significantly increased the risk of developing SLE (OR=2.3, 95% CI=0.9-5.8). Transmission of infectious agents leading to the polyclonal activation of numerous lymphocytes could explain this increased risk. This supports the conjecture that our patient’s disease was caused by the blood transfusion she had received prior to admission.

Corticosteroids are the prescribed treatment for SLE, often in combination with immunosuppressants if the patients are unresponsive to corticoids alone. Management of gangrenous lesions involves cleansing using sterile techniques, removal of necrotic tissue, and in severe cases amputation of the digits or toes once demarcation had been completed. Since this patient presented with progressive necrosis and auto-amputation of the foot with a developed demarcation, she was recommended surgery. Currently, several biological treatment options are being explored for JSLE in modern medicine including blockade of IL-6 signalling and inhibition of TNF-a in patients with JSLE and arthritis. Interleukin-17 plays a central role in the development of tissue inflammation through chemo-atraction of additional immune cells. Effector T cells are the main source of IL-17, and IL-23 plays a role in their priming. Thus, blockade of IL-17 or IL-23 may be beneficial in JSLE. Moreover, the development of biomarkers has been prioritised as one of the principle research priorities in JSLE undertaken by the Lupus Foundation of America with urinary biomarkers for lupus nephritis currently being one of the most active areas of biomarker research internationally.

**Conclusion**

This case presented a unique diagnostic challenge as not only is JSLE a rare disorder but the patient displayed no other commonly associated clinical manifestations. Absence of a single reliable and specific laboratory investigation for SLE makes it a diagnosis of exclusion based on the patient’s symptoms in conjunction with a multitude of other investigations. Physicians need to be trained to swiftly identify rare presentations of SLE lying outside the typical diagnostic criteria, so as to maximise the patient’s chances of recovery.

**Declaration:** Consent to Participate: Informed consent for publishing the case was taken both from the patient and her mother.

**Disclaimer:** None to declare.

**Conflict of Interest:** None to declare.

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