Necrotizing Polyarteritis Nodosa-like Vasculitis in a Child with Systemic Lupus Erythematosus

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A 10-year-old child presented with prolonged fever, lymphadenopathy, weight loss, oral ulcers, alopecia and parotitis. She later developed arterial thrombosis, poly-serositis, nephritis, myocarditis, sacro-ilitis, autoimmune hemolytic anemia and refractory thrombocytopenia. Though anti-dsDNA was negative, she was diagnosed to have systemic lupus erythematosus (SLE). Terminally, she had pulmonary symptoms and succumbed to her illness. The autopsy showed lupus nephritis-Class II, polyserositis, myocarditis, inflammatory myositis, immune mediated vasculitis involving renal, coronary, pancreatic, adrenal, dermal and intramuscular arteries, and pulmonary hemorrhages and edema.

Keywords: *Fever of unknown origin, Lymphadenopathy, Thrombocytopenia.*

CLINICAL DISCUSSION

Clinical discussant: A 10-year-old girl presented with fever of one year duration, cervical and submandibular lymphadenopathy for nine months, generalized swelling for four months, breathlessness for one month, and pain in both hands for a week. There was history of excessive loss of hair, recurrent oral ulcers, and progressive weight loss for the past one year. However, there was no photosensitivity, joint pains, or history of contact with tuberculosis (TB). Computed tomography (CT) chest done three months ago showed necrotic mediastinal and axillary nodes for which anti-tubercular therapy (ATT) was started. The birth, family, development and immunization histories were non-contributory.

Examination revealed tachycardia, tachypnea, low volume upper limb pulses and systolic hypertension in three limbs. She had pallor, anasarca, bilateral parotid enlargement and generalized lymphadenopathy, including epitrochlear and occipital lymph nodes. Abdomen was tense on palpation, with fluid thrill and hepatomegaly. Fine crackles were heard on the left side of chest. Examination of the nervous system and fundus were normal.

Provisional diagnosis of disseminated tuberculosis was entertained with other possibilities of human immunodeficiency virus (HIV) infection, systemic lupus erythematosus (SLE), systemic vasculitis and lymphoreticular malignancy. In view of weak peripheral pulses, Takayasu arteritis (TA) was also considered. Investigations at admission revealed hemoglobin 8 g/dL, total leukocyte count 12.8×10^9/L, and platelet count 120 $\times10^9$/L). During her five weeks of hospital stay, she had hemoglobin between 7 and 10 g/dL, and the lowest platelet count was 87×10^9/L (***Table* I**). Anti-nuclear antibody (ANA) was positive, anti-dsDNA equivocal and work-up for TB and HIV was non-contributory. Ultrasonography of the parotids was normal. Chest and abdominal CT confirmed mediastinal and retro-peritoneal lymph nodes with pleural effusion, pericardial effusion and massive ascites. Bone marrow aspiration and trephine biopsy was normal. She developed dry gangrene in two fingers in right hand with proximal progression. A CT angiography of peripheral limb vessels was done.

Radiologist: First CT chest (3 month before admission): Axial sections from the upper thorax revealed multiple discrete lymph nodes (axilla and paratracheal). There was no necrosis, rim enhancement or calcification. There was no evidence of pleural or pericardial effusion. At admission, CECT chest and abdomen revealed multiple axillary, mediastinal and subcarinal enlarged lymph nodes. Main pulmonary artery was dilated compared to the ascending aorta, suggesting pulmonary arterial hypertension (PAH). Mild pericardial effusion and bilateral minimal pleural effusion was noted. Lung windows were unremarkable. Sections through upper abdomen revealed hepatomegaly, normal kidneys, and a bulky pancreas normal in outline and attenuation. Multiple discrete lymph nodes in the mesentery and retro-peritoneum were noted with moderate ascites. CT angiography of bilateral upper limbs showed normal arch vessels (Coronal reformed images 3D reconstruction). There was long segment occlusion of the left brachial

TABLE I: INVESTIGATIONS OF THE PATIENT AT FIRST ADMISSION

Blood counts	Hb: 7-10 g/dL; TLC 16-28 $\times 10^9$/L; Platelet count: 87-250 $\times 10^9$/L
Liver and renal functions	AST 42, ALT 50, ALP 181, Albumin 1.8, Bilirubin 0.7, urea 55, Creatinine 0.7
HIV ELISA	Non reactive
Serology	Parvovirus B19, EBV, Mycoplasma Negative
ANA	3+ mixed (peripheral and diffuse)
Anti-dsDNA	33 (<35)
*C3 (mg/dL)	35 (50-150)
*C4 (mg/dL)	<4 (20-50)
*Direct Coombs' test	Positive with IgG and C3d
Antiphospholipid antibodies	ACA –ve, LA +ve, α_2GP1 –ve,
Skin biopsy	Lymphomonuclear cells in dermis. Immunofluorescence: IgG deposit at dermo-epidermal junction 2-3+, IgA 2+, C3 Negative
FNAC	Reactive hyperplasia; no evidence of malignancy or Kikuchi disease
Bone marrow biopsy	Normal

AST: Aspartate aminotransferase, ALT: Alanine aminotrasferase, ALP: Alkaline phosphatase, ACA: anti-cardiolipin antibody, LA: lupus anticoagulant, FNAC: fine needle aspiration cytology.
**Values in parenthesis indicate normal laboratory range.*

artery and distal reformation of the radial and ulnar arteries. Similar finding was noted on the right side.

Clinical discussant: She was administered intravenous pulse methyl prednisolone for 5 days, followed by oral prednisolone, with initial clinical improvement. She also received supportive care with albumin, transfusions and antibiotics. Few days later, she developed microscopic hematuria and nephrotic range proteinuria. She also developed features of cardiac failure and echocardiography revealed left ventricular systolic dysfunction and pericardial effusion. Considering disease activity, she received another 3 days of intravenous methyl prednisolone and first dose of injection cyclophosphamide. She improved over 5 weeks and was discharged on oral prednisolone, antihypertensives, hydoxychloroquine, low molecular weight (LMW) heparin and aspirin along with daily dose regimen of antitubercular therapy (ATT). Within 6 weeks, she returned with bilateral hip and back pain of short duration. There was tenderness and restricted movements of hips. Bone scan was suggestive of sacro-ilitis (R>L). She received 2nd dose of cyclophosphamide and was discharged.

Two months later, she was admitted with thrombocytopenia and hypo-complementemia which was treated with three pulses of intravenous methyl prednisolone, and 4th dose of injection cyclophosphamide was administered. After three weeks, she presented with skin bleeds and periorbital puffiness with cushingoid habitus. At this admission, she had a platelet count of only 5 $\times 10^9$/L on multiple occasions. ATT was withheld because of transaminitis. International Normalized Ratio (INR) was 1.0. Urine examination was normal. Doppler revealed partial recanalization of the obstructed brachial arteries. Anti-dsDNA was 28 IU/ml (Normal <35). Immunoblot assay showed multiple antibodies including anti-Sm, anti-nuclear-riboprotein, anti Ro and anti La, but Scl 70 and anti-histones were negative. In view of refractory thrombocytopenia, she received a dose of intravenous immunoglobulin (IVIg).

Two weeks later, she presented with fever, irritability, drowsiness and pain in both thighs. She also had features of circulatory collapse with tachycardia and tachypnea. She was noted to have pus oozing from the left thigh. Systemic examination was normal. Clinical impression was of SLE with septic shock and pyomyositis. A possibility of intracranial bleed or neuropsychiatric lupus was also considered. Non-contrast CT head was normal. She was resuscitated with fluids and inotropes which led to clinical improvement; inotropes were tapered and stopped by next 24 hours. She also received multiple antibiotics. USG of thighs did not reveal any pus collection and hip was normal. Blood culture grew *Streptococcus pneumonia*e. She developed massive pulmonary hemorrhage and cardiac arrest.

Unit's Final Diagnosis: SLE with bilateral brachial artery thrombosis, myocarditis, lupus nephritis, bilateral sacroilitis, refractory thrombocytopenia with death attributed to acute massive pulmonary hemorrhage.

Investigations

Anti-dsDNA is positive in 50-75% of the lupus patients

and negative anti-dsDNA does not exclude lupus. In the presence of SLE and arterial thrombosis, one must consider the possibility of antiphospholipid syndrome (APS). Both primary and secondary APS are seen in children, and SLE is the most common cause of secondary APS. One-fourth of the primary APS turn out to have SLE if followed for a long duration. Many (20-90%) children with SLE have anti-phospholipid antibodies. To make a diagnosis of APS, these tests should be positive atleast twice 12' weeks apart, but the second set of tests could not be performed in the index child because she was on anticoagulation therapy. To summarize, the arterial thrombosis in this child was likely to be a secondary APS in the setting of SLE.

Generalized lymphadenopathy in SLE at presentation is seen in few patients. Kikuchi disease is a differential diagnosis in this setting. This may clinically and histologically masquerade SLE; however, presence of autoantibodies rules out this disorder. Sacro-ilitis has been found in 1/6th of the cases, but is usually noted after a prolonged period of SLE. Pulmonary hemorrhage is rare, seen in only 1-2 % of childhood series and slightly more common in adults. In the index child, hemorrhage was most likely secondary to thrombocytopenia; however, in the setting of immunocompromised state, invasive fungal infections like aspergillosis or mucormycosis cannot be ruled out.

On analysis, we have a 10-year-old girl with prolonged fever, lymphadenopathy, weight loss, oral ulcers, alopecia, and parotitis; who later developed arterial thrombosis, polyserositis and renal involvement; myocarditis and sacro-ilitis along with autoimmune hemolytic anemia, and later refractory thrombocytopenia. The entire course put together supports the diagnosis of SLE with 4 of 9 clinical criteria and both the immunological criteria being positive as per American College of Rheumatology (ACR) criteria for diagnosis of SLE. As per the new SLE International Colloborating Clinics (SLICC) criteria for SLE, almost all of them were positive in this child and hence diagnosis of SLE does not seem to be doubtful. Antibody profile showed almost all of the antibodies present in SLE except anti-dsDNA.

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Pediatrician 1: Anti-Smith antibody was positive in the index case, which is highly specific for lupus. Index child satisfied atleast 10 of the 17 new SLICC criteria, but I must remind these are classification and not diagnostic criteria. Arterial thrombosis has been reported in pediatric lupus but less commonly, and is probably secondary to APS in the index child. Anti-dsDNA antibodies may be consumed during active lupus and thus may be negative. In the setting of ANA+, dsDNA- and anti-Ro+ in a child with lupus, inherited complement deficiency should also be thought of.

Physician 1: Although we are dealing with SLE, but there are several unusual features: (*i*) despite the child receiving 4-5 pulses of cyclophosphamide, the disease remained active, so either this is refractory lupus or there is something else; (*ii*) leukocyte counts in a child with lupus would be low or normal; but in the index child they have been consistently high, possibly contributed by infection; and (*iii*) sacro-ilitis would favour a diagnosis of TB involving the sacro-iliac joint.

Pediatrican 2: The patient had refractory thrombocytopenia despite cyclophosphamide, methyl prednisolone pulses and IVIg. I wonder whether there was underlying thrombotic thrombocytopenic purpura (TTP). TTP is well associated with SLE. The neurological manifestations which were described pre-terminally in this patient along with renal involvement and thrombocytopenia could possibly be TTP co-existing with SLE.

Chairperson: The natural course of TTP in SLE is not so. This child had a follow-up of 6-8 months with persistent thrombocytopenia, and the renal failure occurred later, which is odd for TTP.

Pediatrician 3: Pediatric lupus in many ways is more of a primary immunodeficiency (PID) than an autoimmune disorder. Younger the child, more likely it is to be a PID. Here we have a patient who is ANA positive, dsDNA consistently negative, and anti-Ro and anti-Sm positive. This is the typical immunological profile seen with C1q deficiency. As C1q also acts as an opsonin, C1q, deficient children are significantly immunocompromised. The terminal pneumococcal sepsis the patient had is also perhaps related to C1q deficiency. Arterial thrombosis due to APS in children with lupus is extremely rare; although venous thrombosis is very well described.

Clinical discussant: Although the question of TB as a diagnosis remains, but with the given clinical picture, course and the outcome, this does not look like primary disseminated TB. SLE could be of primary immune-deficiency type and there is data to show children and adults with SLE have a completely distinct antibody response to common viral infections; and there are studies which show that affection with measles, mumps or rubella in the first year of life seems to predispose people later on to develop antinuclear antibodies and SLE. The overall picture suggests active lupus which was relentless, and this child probably would have responded to monoclonal antibodies depleting the B cells.

PATHOLOGY DISCUSSION

Partial autopsy was performed on this young girl and polyserositis *i.e.* pleuritis, pericarditis and 500 mL of ascitic fluid were documented. Both the kidneys (weight 180 g) were blotchy and cut surface showed small hemorrhagic infarcts and patchy congestion. Renal arteries were palpated and dissected. No nodularity was palpable and ostia of both the renal arteries were patent. One of the branches of left renal artery (extra renal) was cord like. Microscopic examination showed mesangio-proliferative pattern in all the glomeruli. There was no endocapillary or extracapillary proliferation. There was no evidence of necrotizing lesions/wire loops/ basement membrane thickening. Tubulo-interstitial compartment showed mild focal lymphoplasmacytic infiltrate. Immuno-flourescent microscopy showed moderate-intense mesangial staining (3+) with IgM, C3, C1q (2+) with IgG. IgA was only mild and mesangial. Both light chains were equally represented. Overall features are of lupus nephritis Class II (***Web Fig.* 1** and **2**). Left renal artery (extra renal) and interlobar arteries (both) and interlobular branches showed lympho-mononuclear infiltrate in the intima and media of arteries with evidence of broken internal elastic lamina (healing inflammatory vasculitis). In some areas, there was fibrosis in the arterial wall with broken internal elastic lamina (healed vasculitis). Intimal surface showed presence of endothelitis, fibro-intimal thickening and superimposed organized thrombi. There were areas with ectatic dilatation of arterial wall; these changes were segmental to circumferential and at different stages of healing in the same artery and other branches with absence of fibrinoid necrosis suggestive of polyarteritis nodosa (PAN). Immunofluorescence showed presence of immuno-globulins (IgG, IgM, C1q, light chains) in these arteries, both in involved and uninvolved segments. Hence, in addition to lupus nephritis there was immune-mediated medium size vasculitis (PAN-like in healing/ healed phase) with secondary thrombosis (***Fig.* 1** and ***Web Fig.* 3**).

Heart was enlarged (weight 219 g), flabby, globular with dull pericardium. There was biventricular dilatation. Histopathology revealed evidence of lymphocytic myocarditis and healed pericarditis. Coronaries showed evidence of healed, healing fibro-inflammatory arteritis with focal fibrinoid necrosis of arterial wall (acute arteritis). Arterial ectasia at the points of loss of internal elastic lamina was present. Superimposed secondary intimal fibro-inflammatory thickening was present with almost complete occlusion at some points. Intra-myocardial branches also showed arteritis and hyperplastic concentric fibrosis. These changes of active healing and healed phases of inflammatory arteritis involving different segments of coronaries at different stages again supported the diagnosis of PAN.

Gastrointestinal (GIT) system was grossly normal. Random sections from different parts of GIT showed evidence of arteritis in submucosal arteries in stomach and small intestine. Branches of superior mesenteric arteries sampled along with pancreatic arteries also had evidence of acute, healing and healed arteritis in interlobular septae with resultant focal edema and focal apoptosis of acinar tissue. Liver (weight 700 g) was grossly and microscopically normal. Adrenal arteries also showed evidence of healed arteritis **(*Fig* 1).**

Lungs (700 g) on gross examination showed diffuse reddish black discoloration of all the lobes of lungs. There were no focal lesions. Overlying pleura was dull. Discoloured areas showed large areas of fresh haemorrhages, oedema and focal diffuse alveolar damage. There was no evidence of capillaritis.

All other organs were grossly and microscopically normal. Sections from psoas muscle samples at the time of autopsy showed inflammatory myositis. Bone marrow showed adequate representation of all hematopoetic elements including megakaryocytes suggesting peripheral destruction of platelets. There was no evidence of infection in any organ.

Final Autopsy Diagnosis

In a 10-year-old girl diagnosed as systemic lupus erythematosis (ds DNA-negative) and recurrent

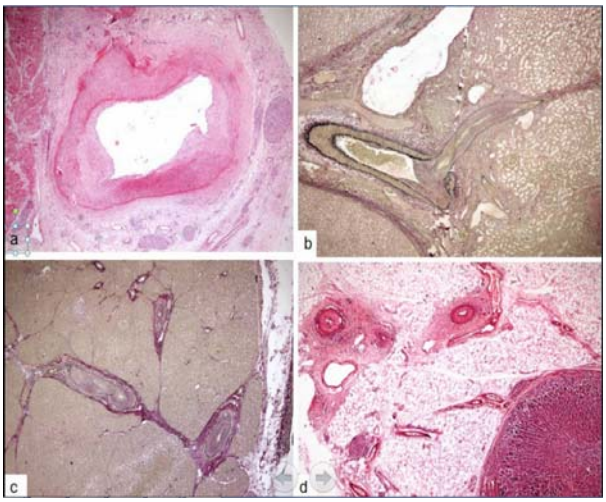

FIG. 1 *Medium size vasculitis in (a) coronary artery, (b) renal artery, (c) superior mesenteric branch in pancreas, and (d) periadrenal artery (H&E a and d, EVG b&c, a-x40,b-d ×20).*

thrombocytopenia with brachial artery thrombosis:

- Lupus Nephritis-Class II
- Polyserositis - Pericarditis, Pleuritis, Ascites
- Myocarditis
- Inflammatory myositis
- Immune mediated vasculitis (medium vessel vasculitis-PAN like) - renal arteries, coronaries, pancreatic arteries, adrenal, dermal and intramuscular arteries
- Pulmonary hemorrhages and edema.

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Pathologist 1: This is an odd case of lupus who had vasculitis like that of PAN, having healed and healing lesions. I do not know whether PAN can co-exist with SLE. The second thing is that with features of myocarditis, coronary artery involvement, intra-mural vessels of the myocardium being involved, the histologist may say these features suggest Kawasaki disease. But the pathologist has rightly described presence of immune deposits in the vessels, which is due to SLE.

Pediatrician 3: In Kawasaki disease, the lesions should be one time; it should not be healed and healing.

Physician 2: In the index case, what takes away the diagnosis of PAN is the presence of immune deposits. But we should all go with the idea that this is the rarest of the rare case, because in the largest series of 676 cases, only 14% had vasculitis of the medium vessels and only 1% had visceral vessel vasculitis involving the medium vessels. If we diagnose such kinds of patients in future, one should consider plasmapheresis, as this is an upcoming treatment in vasculitis with lupus.

*Pathology discussant***:** According to the latest classification scheme, this child had immune-mediated vasculitis involving the medium sized vessels, PAN-like.

Chairperson: If you would like to dissect in depth, we could say this is case of medium vessel vasculitis in patient with SLE; and is most likely related to SLE and one should not call it PAN with SLE.

DISCUSSION

Vascular involvement in SLE was first described by Appel, *et al*. [1], who categorized it morphologically as (*i*) non-complicated vascular deposits of immune complexes, (*ii*) no inflammatory necrotic vasculopathy, (*iii*) thrombotic microangiopathy, and (*iv*) true lupus vasculitis. According to New Chapel Hill consensus system of nomenclature of vasculitis, these would be categorized as immune complex-mediated vasculitis, further defined by the size of the major arteries involved [2].

Of all lupus vasculitis, more than 60% is leucocytoclastic inflammation, 30% is vasculitis with cryoglobulinema, and systemic vasculitis resembling PAN constitutes about 6% of SLE vasculitides patients. Clinical presentation varies from mild forms presenting as purpura, urticarial lesions or bulbous lesions of extremities, and livedo reticularis on the trunk to severe forms with involvement of the internal organs.

Lupus vasculitis in internal organs affects renal glomeruli, pulmonary alveoli, coronaries and cerebral vessels and less often the gastrointestinal tract. Lung vasculitis results in necrotic alveolar capillaritis presenting as pulmonary hemorrhage. In series of 670 patients by Ramos, *et al*. [3] vasculitis was documented in 11%; majority (86%) had small vessel vasculitis (SVV) followed by 14% medium-sized vessel vasculitis (MVV). SLE patients with MVV had a higher prevalence of mononeuritis multiplex (54% *vs*. 2%; $P<0.001$), visceral vasculitis (100% *vs*. 5%; $P<0.001$), and ulcerated/ischemic cutaneous lesions (36% *vs*. 11%; $P=0.047$) and a higher percentage of surgical interventions (45% *vs*. 0%; $P<0.001$) compared with patients with SVV [3].

The present case documents immune complex-mediated vasculitis in pediatric lupus with predominant involvement of medium size arteries with morphologic pattern that of PAN, which is one of the rarest morphologic pattern in lupus. Necrotizing vasculitis with active/inactive glomerular lesions is reported very infrequently (0.3-2.5%) [1,4,5,7].

In a cohort of 341 Chinese patients with lupus nephritis, Wu, *et al*. [7] reported 279 patients who had single or multiple renal vascular lesions affecting the renal outcome. This group has recommended inclusion of renal vascular lesions in the 2003 ISN/RPS system for classifying lupus nephritis to improve renal outcome predictions.

As C1q deposits were noted in glomerular lesions, C1q deficiency is unlikely in the index case.

In this report, we described a 10-year-old girl who succumbed to SLE and its complications. Autopsy revealed PAN-like lupus vasculitis, which is extremely rare in children with SLE.

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