Digital Vascular Manifestations in S.L.E.: A Case Report and Review of Literature for Prognostic Evaluation of Cardiovascular Manifestations in S.L.E.*

S.M.A. BABAR
N. AKHTAR

SUMMARY

A young patient was seen at our Department of Vascular Surgery with secondary Raynaud's disease of a short duration, characterised by digital ischaemia of upper and lower limbs. Family history was positive. Investigations revealed presence of collagen disease. The most likely diagnosis was Systemic Lupus Erythematosus. The patient was treated with steroids and responded well by clinical (loss of symptoms and signs) and laboratory parameters (Falling ESR, lowered C3 and improved digital circulation on doppler flow studies). Since the cardiovascular manifestations are prognostically important in the overall management, appropriate literature was reviewed and quoted here.

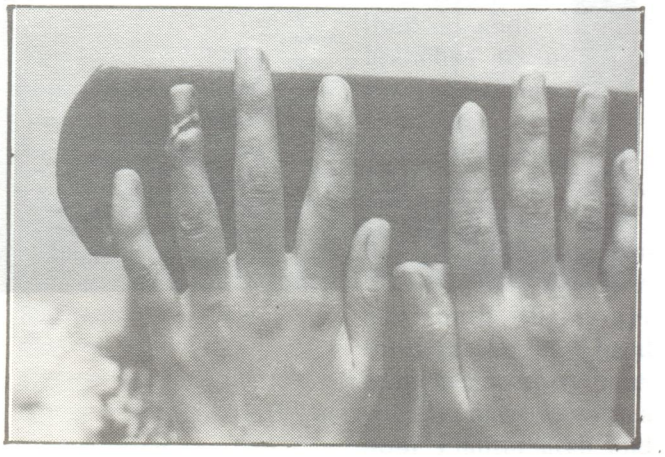
CASE REPORT

RAR, a young 20-year old unmarried female student, in March, 1988, developed intermittent spontaneous cyanosis and later, blackening of her ring finger (left hand), followed 2 days later, with ischaemic intermittent pains, cyanosis of the same finger and similar pain and discoloration of the 2nd and 3rd toes of both feet.

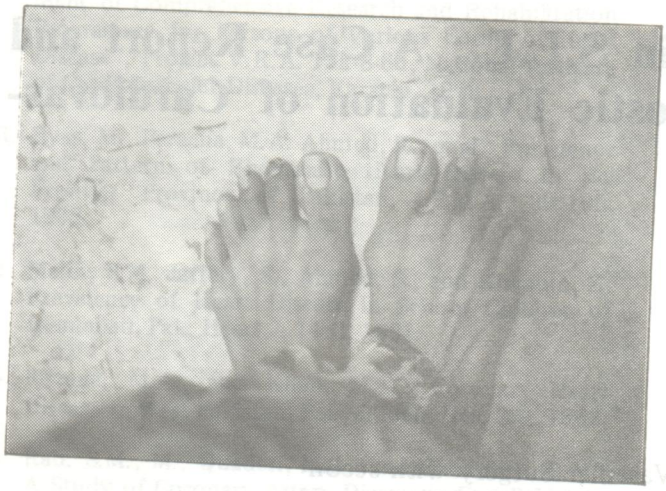
18 months earlier, she had developed a high grade fever for a week followed by painful small joint swellings, which resolved spontaneously after 14 months. She then developed intermittent discoloration of the tip of her left ring finger, associated with coldness, prickling and tingling sensation in the entire finger. The pain and cyanosis did not become worse with contact with cold water.

Her father had suffered from a similar disorder which resulted in autoamputation of two digits in his left foot, 4 years earlier. One sister had been suffering from joint pains for 3 years. She was a non-smoker.

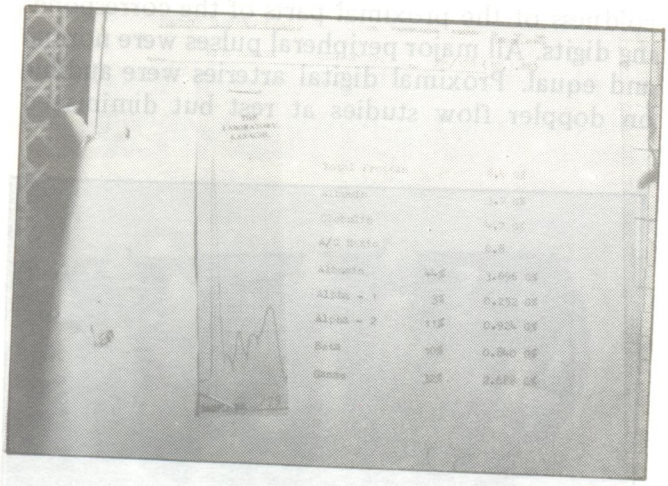
On admission, she presented with dry gangrene overlying the distal phalanx of her left ring finger (see Figure 1), the tips of the second and the third toes on both sides (see Figure 2) and coldness of the proximal parts of the corresponding digits. All major peripheral pulses were normal and equal. Proximal digital arteries were audible on doppler flow studies at rest but diminished



*Dept. of Vascular Surgery Dow Medical College and Civil Hospital Karachi, Pakistan.



with modified Adson's exercise (opening and closing of the hand at the rate of 60/min, with the arm abducted to 110 degrees and extended to 20 degrees with the palms facing the examiner). Cervical ribs were absent and no other bony lesions were found clinically and radiologically in the thoracic outlet region. Her cardiac rythm was normal and she was clinically euthyroid. From time to time she reported cyanosis of her affected fingers occasionally on exposure to cold, but sometimes also spontaneously.



INVESTIGATIONS

Haemoglobin	= 116.6 G%	ESR (West)	= 108mm 1st hr
RBCs	= 3.9 mill/mm^3	WCC	= 12400/mm^3
Polymorphs	= 69%	Lympho	= 22%
Eosinos	= 6%	Platelets	= 100000/mm^3
Blood Urea	= 31mg%	Blood sugar	= 118mg% random
T3	= 0.7 ng / ml	T4 = 2.5 ng / 100ml	
Electrolytes	= Normal	PT = 12/12 sec	
APTT	= 30 / 30 sec	T. Proteins	= 8.4 G%
Albumin	= 3.7 G%	Globulin	= 4.7 G%
ANA	= Positive	RA	= Pos (1:20)
LE cells	= Negative	Anti DNA Ab	= Pos (15 U/ml)
C3	= 0.56 G/1	Anti ds DNA	= Pos (20.3U/ml)

Electrophoresis: (see Figure 3)

Albumin	= 44 % (3.696 G%)
α 1	= 3 % (0.252 G%)
α 2	= 11 % (0.924 G%)
β	= 10 % (0.840 G%)
γ	= 32 % (2.688 G%)

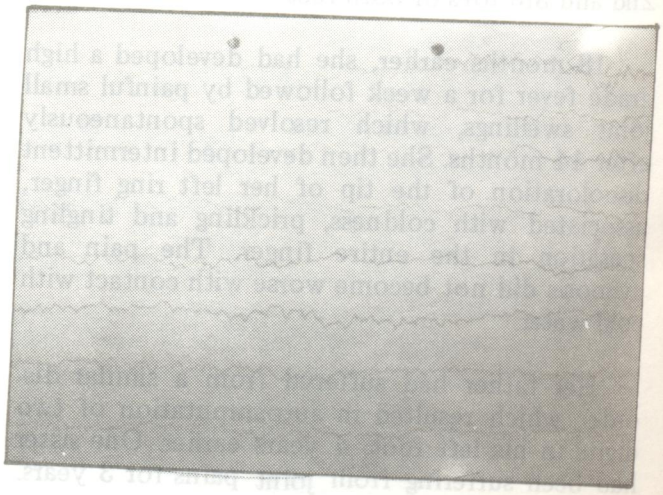
Urine Bence Jones Proteins = Negative (Bradshaw and Hellers)

Chest X-ray = No abnormality detected

Thoracic Inlet X-ray = No cervical rib or other bony lesions were seen

ECG = Sinus arrythmia seen. No other abnormalities seen.

EEGs = Diffuse non specific activity seen on both sides.
No α activity was seen (see Figure 4)



Temporal artery biopsy:

Temporal artery biopsy was normal showing no evidence of arteritis Elastic lamina was intact and there was no inflammatory infiltrate in the wall of or around the artery.

Angiography:

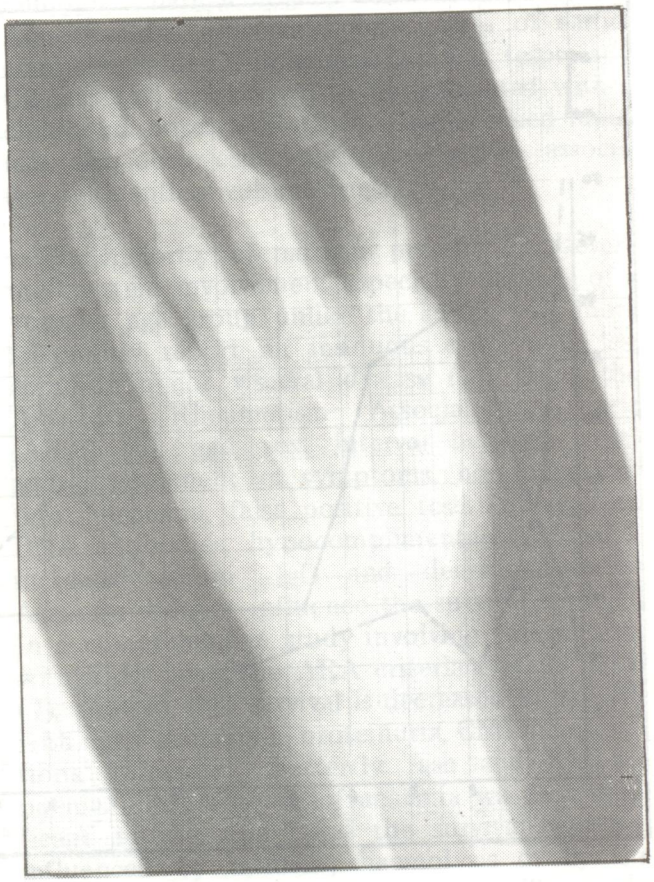
Seldinger, Right Femoral route, Four limbs + Renal angiograms.

– Both Renal arteries = Normal in origin, diameter and branches.

– Left Upper limb = Left radial artery was diffusely narrow in comparison to the Ulnar artery with delayed filling. No localised lesion was seen. The Superficial Palmar arch was seen predominantly filling from the Ulnar artery. Digital arteries were not visualised in any fingers.

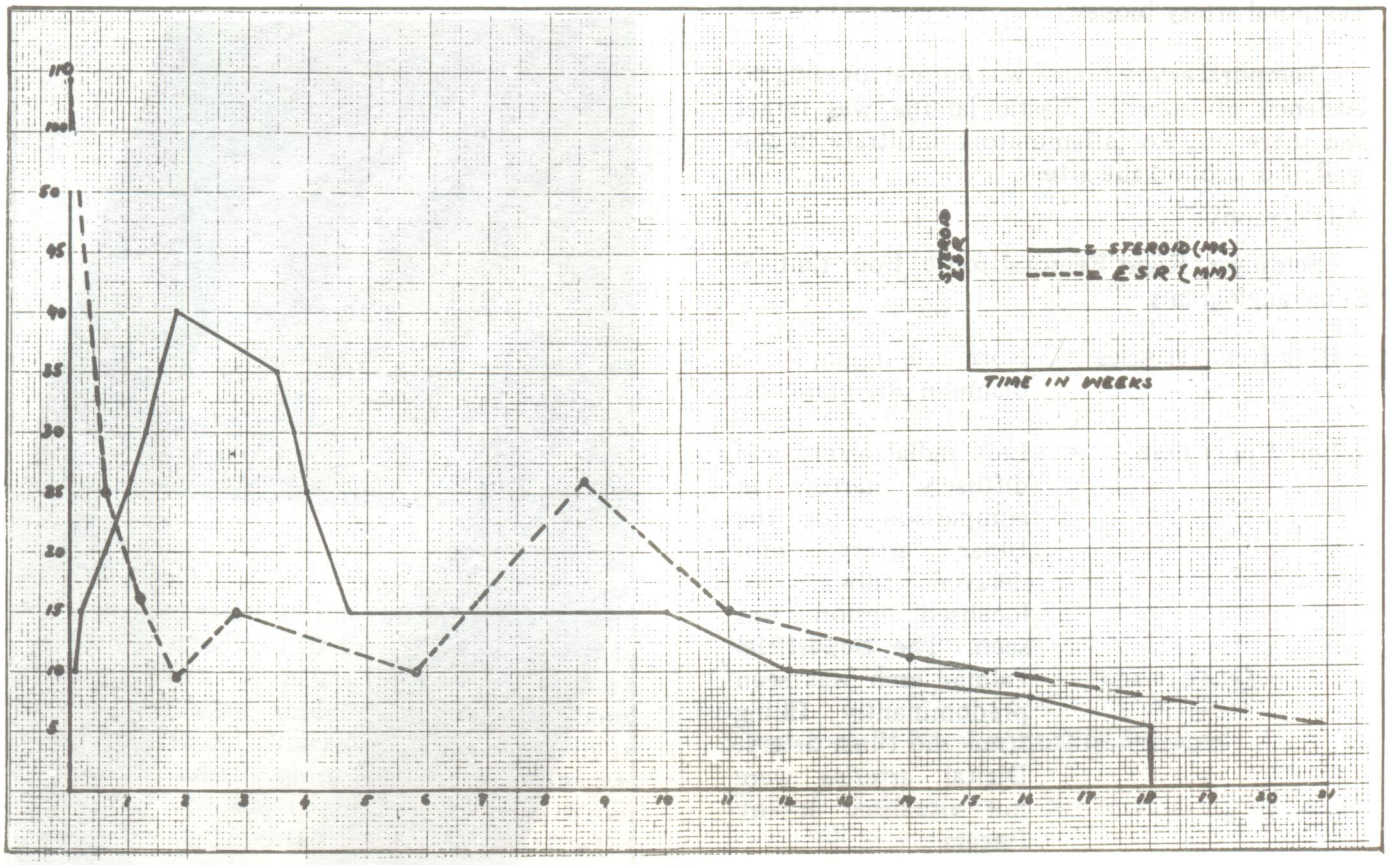
– Right Upper limb = Radial artery was diffusely narrow without any localised lesions, but with delayed filling. The Superficial Palmar Arch showed delayed filling from Ulnar artery. Metacarpal branches were normal. Digital branches to the Middle, Ring and the Little fingers were visualised but the thumb (see Figure 5).

– Left lower limb = The Common Femoral, Profunda femoris and the Superficial Femoral Arteries were normal. Aortic bifurcation was normal. The Popliteal and its trifurcation were normal. In the lower third of the leg the Anterior tibial artery was narrow.



Posterior Tibial and the Peroneal arteries were similarly narrow from this level downwards. The Plantar arch was poorly visualised and digital branches to none of the toes were outlined. Dye clearance was delayed suggesting narrowing of distal vessels.

– Right lower limb = All of the there popliteal branches were normal until the lower third of the leg. Distal branches were symmetrically narrow with a poor Plantar arch and absent digital vessels.



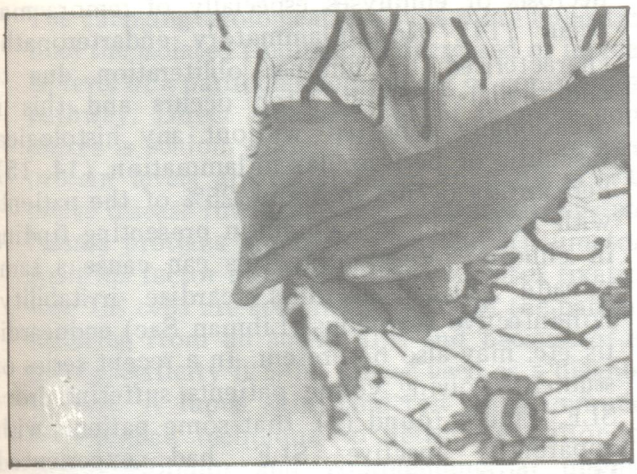
MANAGEMENT

Prior to the availability of the laboratory results, empirical treatment was started with dipyridamole 50 mg t.d.s, aspirin 150 mg daily and Nifidipine 5 mg q.i.d. The attacks of intermittent cyanosis did not diminish in the ensuing 72 hours. Buflomedil, a vasoactive drug, was then substituted for Nifidipine, in the dose of 300mg q.i.d. The attacks became less severe but the frequency remained uncharged.

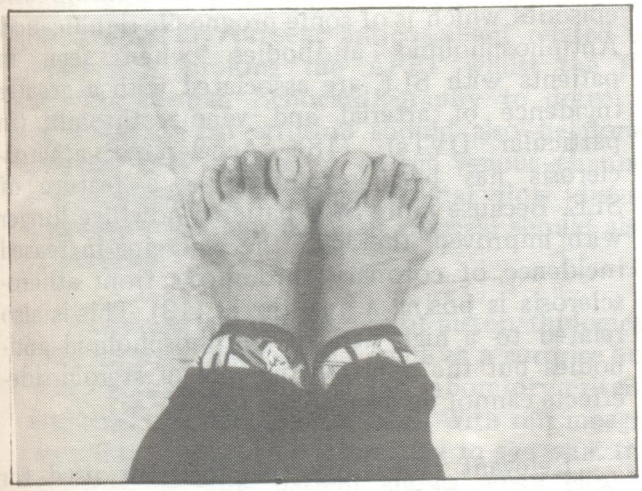
When the diagnosis of collagen disease was confirmed, treatment with steroids was commenced. Serial estimation of ESR was then carried out. The steroid dosage was built up over a two-week period, maintained for two weeks and then tapered to a maintenance dose which was based on symptoms-improvement and on reduction of ESR. Prophylactically she was also given cimetidine 400mg nocte and did not report any dyspepsia. She developed cushingoid facies but no electrolytic disorders. With reduction of steroid dosage the facies became normal. (see Figure 6).

Her pains were fully suppressed on the maintenance dose of steroid. The upper limb cyanosis disappeared and the dry gangrene began to autoamputate aseptically. The lower limb toe cyanosis were fully resolved and she continued to walk normally. The hand with the gangrenous finger was kept dry by the patient but the other hand was allowed to come into contact with cold water and ice from time to time. This did not reproduce her pains or cyanosis. At the end of twelve weeks the gangrenous finger became autoamputated without any real disability or sepsis (see Figure 7). The toe discoloration cleared up fully (see Figure 8) and she resumed using her regular shoes.

Modified Adson's test was repeated 12 weeks after commencement of steroid therapy which at this stage was negative. Cold provocation test was also negative for all of the limbs. Doppler revealed reformation or renewed flow in the digital vessels of all fingers and toes.



Steroids were finally stopped 18 weeks after institution of therapy on the assumption of steroid-related remission. Her serial ESRs remained below 10. She continues to remain on our follow-up programme.



DISCUSSION

SLE is a fairly uncommon illness affecting girls 5 times more than boys although the striking female predominance is not seen until after puberty. Before puberty, the ratio of girls to boys is lower, approximately 3:1 (1, 2). In the USA, the incidence is 4 times higher in the negroid population although the same predominance has not been seen in Africa (1). The incidence has recently risen most probably due to increased awareness and to improved diagnostic methods. A recent Baltimore study showed the incidence to be 4.6 per 100,000 population per year (16). There is still a considerable controversy about the possible aetiological factors and these include humoral, pharmacological and infective agents. Abnormalities especially, deficiencies of earlier components of Complement pathway (especially C2 and C4) are known to be associated with a childhood onset SLE (3,4). Drug-induced lupus may also occur especially in children in association with anticonvulsant drugs (5).

The majority of patients present with severe multisystem involvement especially patients of a younger age group unlike the adults who more frequently report an insiduous onset with less common major visceral disease (2). Using the American Rheumatism Association Criteria (ARA) (6), age, sex, interval between onset and development of symptoms, non infectious fever, anaemia, false positive tests for syphilis, DNA antibodies, hypocomplimentaemia C2,3,4, increased serum IgG and decreased serum Albumin did not influence the survival rate (7). In a comprehensive study involving 148 patients with SLE, using the ARA criteria Holberg et al (7), showed that survival is decreased in patients with early azotaemia, proteinuria, CNS manifestations, infections, butterfly rash and lymphopoenia. The influence of anaemia was not significant in the study and the survival was not influenced by arthritis, haemolysis or by the presence of Raynaud's phenomenon. The study also showed that the anti DNA and various serum protein abnormalities (C2,3,4, IgG and albumin) had no predictive importance for the survival. Severe non fatal infections (meningits, septicaemia, pneumonia) were predictors of increased SLE-related mortality. Two thirds of the patients with such infections in the study described above, during the first two years of observation, died. The causes of death were attributable to the causative factors related to SLE. Nephropathy was a predictor of SLE related mortality whereas CNS manifestations had no significant effects on survival (7,8). Dimant et al (8), found a lower mortality in patients with than without Raynaud's phenomenon. Lymphopoenia (significantly co-existing with nephropathy) (9) was a predictor of increased SLE related mortality whereas the presence or absence of DNA antibodies and hypocomplimentaemia C3 and 4, had no predictive value for survival (7). Other studies have also shown DNA antibodies to be without influence on survival (10, 11) although some other studies have shown in the past that persisting high titres or rising titres of DNA antibodies increased the risks of flare-ups whereas persisting

hypocomplimentaemia had no prognostic value.

The clinical manifestations of SLE include weight loss, anorexia, malaise, fatigue and fever, however, often the fever is caused by a superimposed infection. Generalised lymphadenophathy and hepatosplenomegaly may also be present (1). Cardiovascular and haematological disorders associated with SLE are fairly important prognostically and also from the point of view of response to steroid therapy. Haematological disorders include anaemia, which is found in about half of the patients and may be the result of destruction of red cells or blood loss. Marrow aplasia is rare. A chronic constitutional anaemia of a normocytic normochromic variety is less common and even less common is a hypochromic microcytic type of pattern. A Coomb's positive antibody-medicated haemolytic anaemia is also possible. Coomb's test may be positive without clinical evidence of a haemolytic anaemia (1). Thrombocytopoenia is medicated by autoantibodies and is present in 75% of the patients suffering from SLE (12). Leucopoenia is present in about half of the patients and may be severe. Antineutrophil antibodies may be responsible for the leucopoenia and for the susceptibility to overwhelming infections. Circulating coagulant factors may lead to a hypercoagulable state and to thrombotic and embolic phenomena. Their presence correlates well with false positive serological tests for syphilis and anticardiolipin antibodies (13).

Raynaud's phenomenon with the typical triphasic colour change reported in the European literature presents in a modified form in Pakistan with a biphasic change. Erythema from digital vasospasm in response to cold or to emotional stress occurs usually in adults and not in children. In its presence other collagen disorders (such as Rheumatoid arthritis, Scleroderma, Mixed Connective Tissue Disease etc.) should be excluded. Raynaud's phenomenon is seen in about 10% of the patients suffering from SLE. This may also be associated with necrotising vasculitis particularly involving the small to medium sized vessels and causing cutaneous ulcerations or necrosis and thromboses in viscera (7). Although it is not quite clear as to why these selective cutaneous lesions occur, the association of high levels of circulating immune complexes is thought to be aetiologically related (14). Ischaemic necrosis of epiphyses especially of femora may occur (14). Non-inflammatory endarteropathy characterised by luminal obliteration due to endothelial swelling often occurs and this is occasionally reported without any histological vasculitis or perivascular inflammation. (14, 15). Pericarditis occurs in about 25% of the patients with SLE, and is a common presenting finding in children. Very rarely this can cause a tamponade (2). Myocarditis, cardiac irritability, non-infective verrucous (Libman Sac) endocarditis etc. may also be present. In a recent series of studies involving young patients suffering from SLE, Emery found (1), that some patients with apparently inactive SLE had experienced Myocardial Infarction. The study also showed that some very young patients had developed diffuse premature arteriosclerosis and vascular scarrings. But her study may have been biased inasmuch as these might have been the effects of prolonged use of steroids. Harris (17) has described a marker in patients with thrombotic episodes which is of some prognostic significance. Antiphospholipid antibodies, when seen in patients with SLE are associated with a greater incidence of arterial and venous thrombi (in particular DVTs), (18). Accelerated atherosclerosis has been recognised as a feature of SLE. Because more SLE patients now live longer with improved therapy, the emerging increased incidence of coronary thrombosis from atherosclerosis is posing a new threat (19). This is also related to a high titre of antiphospholipid antibodies but the contributing role of steroid side-effects cannot be overlooked (20).

Relevant laboratory investigations used for diagnosis of SLE in complicated disorders involving cardiovascular system, include the following:

The best single screening test for SLE is the test for antinuclear antibodies. This is not specific for SLE and can be positive in other collagen disorders. The most useful specific test is the isolation of specific antibodies to double stranded native DNA. This is relatively specific to SLE and its titre correlates well with more severity of disease and multisystemic involvements. Complement levels are usually low in the active phase. CH50 is an ideal modality to test but because of technical difficulties and cost, an estimation of C3 and C4 is appropriate and reflects the general state of complement system in the diseased state.

The changing serological levels are more important than the isolated finding of a decreased or increased level of a particular component of complement pathway. Direct measurement of immune complexes is seldom done. The ESR and 'C' reactive protein levels are often raised in patients with active disease involving the cardiovascular system. Plasma proteins are fairly high and Rheumatoid Arthritis factor may be positive on latex fixation test. LE cells are seen in only 50% of the patients suffering from an active SLE and because of its poor specificity it is no longer used as a diagnostic test. A lupus skin band test using immunofluorescence technique to detect deposition of immunoglobulin and complements at dermal-epidermal junction was at one stage thought to be pathognomonic of SLE but has now been found to be falsely positive in some other collagen disorders as well. Because autoantibodies to red cells and platelets are frequently present in SLE, a screening Prothrombin time, APTT, platelet count and platelet function tests should be done. An abnormally present anticoagulant related to lupus may prolong the APTT whilst the PT remains normal. Echocardiography to detect a small pericardial effusion should also be done. Doppler flow studies to detect venous channel abnormalities (DVT) and arterial flow disturbances (in medium to small arteries) should also be assessed.

In our patient the absence of histopathological inflammatory findings did come as a surprise but other clinical, behavioural and laboratory criteria suggested the diagnosis of SLE. With our meagre resources, it would be interesting to see what the follow-up in this patient shows when clinical parameters are adjusted against a changing ESR and C3 level. If consistent improvement is reflected by corresponding ESR and C3 changes then a cheaper and relatively reliable method would have become popular in Pakistan to assess the progress of SLE treated with steroids.

REFERENCES

1. Emery H. Clinical Aspects of Systemic Lupus Erythematosus in Childhood. Paediatric Rheumatology. Paed Clin of N. America. 1986: 33:5, 1177-1190.
2. King K et al: The Clinical Spectrum of SLE in Childhood: Arthritis Rheumat: 20:287-294, 1977.
3. Kjellerman M et al: Homozygous deficiency of C4 in a child with lupus erythematosus syndrome: Clin. Gen: 22(6): 331-339, 1982.
4. Schaller J et al: Severe SLE with Nephritis in a boy with deficiency of the fourth component of Complement: Arthritis Rheum: 20: 656: 1977.
5. Singsen BH et al: Antinuclear antibodies and lupus like syndromes in children receiving anticonvulsants: Paediatrics: 57: 529, 1976.
6. Tan EM et al: The 1982 Revised criteria for the classification of SLE: Arthritis Rheum: 1982: 100, 714-727.
7. Halberg P et al: Systemic Lupus Erythematosus. Follow Up study of 148 patients. Clinical Rheumato: 1987: 6, (1), 22-26.
8. Dimant J et al: The Clinical significance of Raynaud's phenomenon in SLE: Arthritis Rheum: 1979: 22, 815-819.
9. Halberg P et al: SLE: Classification, clinical and lab findings, course and outcome. 148 cases: Clin Rheumatol: 1987: 1, 13-21.
10. Davis BM, Gillam JN: Prognostic significance of subepidermal immune deposits in uninvolved skin of patients with SLE: Invest Dermatol: 1984, 83, 242-247.
11. Fries JS, Hilman HJ: SLE: A Clinical Analysis: Philadelphia, WB Saunder and Co: 1975, 110.
12. Wallace C et al: A prospective study of childhood onset SLE. Arthritis Rheumatol: 21: 590-600, 1978.
13. Bernstein ML et al: Thrombotic and haemorrhagic complications in children with lupus anticoagulant: Am J Dis Child: 138: 1132-1135, 1984.
14. Fink CW: Vasculitis: Paediatric Rheumatology: Paed Clin N America: 33 (5), 1986, 1203-1219.
15. Crowe WE et al: Clinical and pathogenetic implications of histophathology in childhood polydermatomyositis: Arthritis Rheumat: 25: 126-139. 1982.
16. Hochberg MC et al: Arthritis and Rheumat: 28, 80-85, 1985.
17. Harris EN et al: Clin and Experim Rheumatol: 2: 47-51, 1984.
18. Hughes GRV et al: Journ Rheumatol: 13: 486-489, 1986.
19. Bonfiglio TA et al: Am Heart Journal: 83: 153-158, 1972.
20. Ridley MG et al: Survival in SLE: Brit J Hospi Med: 39 (3), 237-41, 1988.