

Clinicopathological Conference of the Postgraduate Institute of Medical Education and Research, Chandigarh.
Editor: B.D. Radotra

Young Girl with Painful Joints and Failing Kidneys

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Clinical History

S, an 11 year old girl presented to the Nehru hospital (CR No. 224747) of Postgraduate Institute of Medical Education and Research (PGI), Chandigarh on December 1, 1995 with 10 months history of joint pains. Her other presenting complaints were fever and cough of 1 month duration, boils on forehead and mouth ulcers of 15 days duration.

In February 1995, she started with pain in small joints of hands and feet but later there was involvement of wrists, ankles

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and knees as well. The pain was not accompanied by swelling, redness or deformity. Despite treatment with analgesics she continued to have intermittent joint pains. In April 1995, she suffered from low to moderate grade fever associated with vague pain over back and chest.

In May 1995, she was admitted at a hospital in Ludhiana with the complaints of continuous fever, pallor, mucosal ulcerations and bleeding gums. Her blood pressure was 110/70 mm Hg. Systemic examination did not reveal significant abnormality. Investigations at that time yielded a hemoglobin (Hb) of 5 g/dl. Her total leucocyte count (TLC) was 4800 per cu mm with a differential count (DLC) of 62% polymorphs and 29% lymphocytes. The erythrocyte sedimentation rate (ESR) was 155. The blood urea level was 32 mg/dl and serum creatinine was 1.5 mg/dl. Widal test was non reactive. The prothrombin time index (PTI) and PTTK were within normal limits. Anti nuclear factor (ANF) and LE cell were positive. She was given 2 units of blood and started on prednisolone. She became afebrile and was discharged. She apparently recovered fully and remained well in July and August. Her parents stopped steroids against medical advice. In October 1995, she had generalized weakness, recurrence of fever, joint pains and ulcers in the mouth. She developed boils on the forehead in late half of November. Her appetite was poor and she used to vomit after every feed. There was also a history of passage of dark tarry stools and intermittent episodes of aggressive behavior, irritability and irrelevant talk two days prior to admission. In the past she had fever for a month about 2 years back. She was fully immunized. She had a female sibling, 6 years old, who was well.

On general physical examination, she

weighed 23 kg with a height of 133 cm. Her heart rate was 120 per min and respiratory rate 25 per min. The blood pressure was 100/60 mm Hg. Capillary filling time was 2 seconds. She was pale and there was generalized edema, alopecia, malar rash, oral ulcers and pustules over forehead and scalp. The chest examination revealed no significant abnormality. Cardiovascular examination revealed a soft systolic apical murmur. On abdominal examination there was no free fluid. Liver was palpable 4 cm below costal margin with a span of 14 cm and the spleen was also palpable (2 cm). On central nervous system (CNS) examination there was no evidence of cranial nerve palsies. Muscle wasting was observed; however, there was no focal deficit. Deep tendon jerks were normal. Fundus examination revealed venous engorgement.

Investigations

The serial hematological investigations and urine analysis are summarized in *Tables I* and *II*, respectively. The prothrombin time was 16 sec (control 12 sec) and PTTK 43 sec (control 37 sec). LE cell, ANF (++++) and anti ds DNA antibodies (strongly positive) were all positive.

Biochemical Investigations

The biochemical investigation revealed: serum sodium varying from 127 to 142 mEq/l, serum potassium varying from 4.5 to 6.5 mEq/l, blood urea varying from 150 to 160 mg/dl, serum creatinine varying from 0.5 to 3.5 mg/dl, serum bilirubin 0.5 mg/dl, SGOT/PT 15/9 IU, serum alkaline phosphatase 18 KAU, total serum proteins 7.1 g/dl, serum albumin 3.4 g/dl and serum calcium 8.5 mg/dl. The serial arterial blood gas analysis are summarized in *Table III*.

Microbiological Investigations

Swab from pustules grew *Staphylococcus aureus* (sensitive to methicillin). Blood culture and endo-

tracheal tube culture did not reveal growth of any microorganisms. Ascitic fluid and CSF cultures were sterile.

Radiological Investigations

The serial X-rays of chest revealed: (i) 2/12: Lung fields clear and cardiothoracic (CT) ratio of 0.55; (ii) 6/12: Bilateral alveolar shadows, CT ratio of 0.63 and pleural effusion was present; (iii) 7/12: Relative clearing of shadows and CT ratio of 0.62.

Other Investigations

The electrocardiogram (ECG) revealed a heart rate of 136 per min with a normal rhythm and axis of 50. The PR interval was 0.16s and QTc interval was 0.48s. The RV was 6-25, and SV was 1-20. There were no ST and T wave changes. On echocardiography there was moderate mitral regurgitation with trivial tricuspid regurgitation. There was global hypokinesia with an ejection fraction of 18%. There was no evidence of vegetations or pericardial effusion.

Ascitic tap showed a protein of 1.5 g/dl and sugar of 180 mg/dl. There were 100 cell per cu mm; 60% of which were polymorphs. The CSF was clear and showed 30 mg/dl proteins and 180 mg/dl sugar with 10 cells (80% polymorphs).

Course and Management

She was given 2 blood transfusions, intravenous fluids, and ranitidine and was started on cloxacillin. Her BP was 110/80 mm Hg and urine output was adequate. On 3/12/ 95 she had three episodes of generalized tonic clonic seizures for which she was given diazepam and dilantin. Cefotaxime was also added in her medication. She had malena and her BP was recorded to be 106/68 mm Hg. Between 4/12/95 and 6/ 12/95 she was given pulses of intravenous methylprednisolone (500 mg) and her blood pressure recovered. She started talking

TABLE I—Summary of Serial Hematological Investigations.

Date (g/dl)	Hb (per cu mm)	TLC	DLC	Platelets (per cu mm)	ESR (mm fall in 1st four)	Peripheral smear
1/12	5.4	7200	P81 L10			Nucleated RBCs Platelets adequate
2/12	8.5	8600	P76 L20			Platelets adequate
4/12	11.1	8200	P77 L20	75,000	42	Reticulocytes 5%
7/12	12.3	12,400	P81 L17			Reticulocytes 6%

TABLE II—Summary of Serial Urine Analysis.

Date	Sugar	Albumin	Specific gravity	Pus cells (per HPF)	RBCs (per HPF)	Epithelial, cells (per HPF)
2/12	Nil	++++	1015	—	4-5	1-2
4/12	Nil	++++	1020	Occasional	1-2	—
8/12	Nil	Nil	—	Rare	Rare	—

HPF-High Power field.

24 h urine protein was 1.5 g.

TABLE III—Serial Arterial Blood Gas Analysis.

Date	pH	PaO ₂	PaCCX,	HCO ₃
6/12	7.50	80	18	14
7/12	7.30	85	25	11.5
8/12	7.50	70	23	20
9/12	7.40	57	21	13
9/12	7.12	38	27	8.5

irrelevantly and also developed ascites. On 6/12/95 her heart rate was 140 per min and BP 90-100 mm Hg systolic. There were bilateral basal crepitations and S3 gallop was also noticed. She had intermittent aggressive behavior. She was shifted to Pediatric Intensive Care Unit. Her central venous pressure was 20 cm. She

was given frusemide and started on dopamine and dobutamine. On 7/12/95 echocardiography was done which revealed global hypokinesia but there was no evidence of pericardial effusion. There was marginal improvement in general status. Pulse cyclophosphamide (along with Mesna) was started and dexamethasone was continued. On 9/12/95 she was put on a ventilator. The hypotension persisted and she had 2 episodes of generalized seizures. An adrenaline infusion was started. However, the hypotension persisted, she developed cardiac arrest and was declared dead at 9 PM.

Unit's Diagnosis

SLE with multisystem involvement.

Differential Diagnosis by Dr. Surjit Singh

There appear to have been 4 distinct phases in this child's illness. She first became unwell in February 1995 when she developed joint pains and constitutional symptoms. She was hospitalized with these complaints at a hospital in Ludhiana in May 1995 where a diagnosis of systemic lupus erythematosus (SLE) was made and the child was started on oral prednisolone. This was followed by a complete symptomatic recovery in August 1995 and at this stage the parents stopped giving her prednisolone against medical advice. Within a few weeks of stoppage of corticosteroids, *i.e.*, October 1995, she again developed constitutional symptoms which progressively worsened. By end of November 1995, her condition deteriorated further and she had evidence of encephalopathy in the form of aggressive behavior, irritability and irrelevant talk.

As far as the primary diagnosis is concerned I have no doubt that she had SLE. In fact I would go as far as saying that there is no other condition which can explain all the clinical findings in this patient. She fulfills 9 out of 11 criteria listed in the 1982 American College of Rheumatology Classification for SLE(1). However, what needs to be looked at now is the pattern and severity of organ involvement which appear to be a little unusual in this patient(2,3). She had involvement of 4 systems, namely, the renal, cardiovascular, CNS and pleuropulmonary.

Coming to the renal involvement first, it is obvious that she had lupus nephritis as evidenced by the presence of microscopic hematuria, nephrotic range proteinuria and azotemia at the time of presentation. If she had lupus nephritis, where would she fit in the WHO classification of lupus nephritis? The fact that she had nephrotic range

proteinuria would suggest that she had either Class IV (*i.e.*, diffuse proliferative) or Class V (*i.e.*, membranous) nephritis. Of these, I would tend to favor the former (*i.e.*, Class IV) because she showed a rather dramatic response to pulse methylprednisolone. I would not expect class V lupus to respond so rapidly. Further, I would think that her nephritis is of recent origin which means that I would not expect signs of chronicity in renal histopathology, namely, features of glomerular sclerosis are unlikely to be present.

This patient showed a rapid reversal of azotemia on administration of pulse methyl-prednisolone. This appears a little odd but there is enough evidence in the literature that this can happen. Similar cases of Class IV lupus have been previously reported (4,5) where the azotemia cleared within a few days of starting mega-dose steroid therapy—a finding which is akin to what appears to have happened in this patient.

Regarding the CNS involvement, this patient undoubtedly had lupus encephalopathy. The clinical presentation of this encephalopathy can be broadly categorized into 2 main groups: (*i*) The stroke syndromes which are associated with the presence of an anti-phospholipid antibody and generally manifest as focal deficits in the form of hemiplegia or cranial nerve involvement. The morphological correlates of this presentation would be infarcts in the CNS; and (*ii*) Diffuse CNS disease which is associated with, amongst others, the lymphocytotoxic antibody, and which generally manifests with neuropsychiatric symptomatology. The morphological correlates of this presentation would be inflammatory exudates and vasculitis in the CNS and that is what I would expect in this patient. The lymphocytotoxic antibody recognizes many different epitopes and

one of these is the CD 29 receptor which is said to be present on both lymphocytes and the neuronal cells.

Now we come to the cardiovascular system involvement which was a little unusual. She had myocarditis as evidenced by persistent tachycardia, cardiomegaly, features of congestive heart failure and evidence of poor contractility on echocardiography. It would be tempting to attribute this myocarditis to the primary disease (SLE) and SLE myocarditis has been well described in the literature. However, what goes against this possibility is the fact that she developed myocarditis while on maximal immunosuppression. One would not normally expect SLE myocarditis to first develop and then progress in this manner under such circumstances. I would, therefore, like to offer an alternative possibility of viral myocarditis, for instance Coxsackie myocarditis. SLE is known to be associated with many subtle immuno-deficiencies and it is possible that our patient developed a viral myocarditis because of this underlying immuno-deficient state. Most normal children would be expected to recover after an episode of viral myocarditis. The fact that this child did not recover could be explained on the basis of a progressive viral infection in a borderline immuno-deficient child.

There is no clinical or laboratory evidence of pericarditis but it would be extremely unusual for SLE myocarditis to occur in absence of pericarditis. On autopsy, therefore, I would expect to find pericarditis. As far as endocarditis is concerned there were no vegetations on echocardiography. But it is possible that the regurgitant lesions in this child were secondary to Libmann-Sacks vegetations occurring on edges of valve cusps. Bacterial endocarditis can occur in association with SLE but I do not think this

was the case in this child. SLE is one of the causes of serious coronary artery disease in children and deaths have been reported because of the associated vasculitis. However, in this child I do not think there was significant coronary artery involvement as there was no evidence of ischemia on ECG and the echocardiographic examination also did not reveal any segmental dyskinesia.

This child also had pleuro-pulmonary involvement. The pleural component was evidenced by pleural effusion. Pulmonary component was, however, more difficult to categorize. It is an axiom in medicine that any parenchymal involvement in SLE patients is due to an infective process until proved otherwise. However, in this patient the temporal course of events suggests that this was not the case. The pulmonary infiltrates cleared remarkably on fluid restriction and diuretic administration and this suggests that the underlying etiology of these infiltrates was pulmonary edema. The term lupus pneumonia is a pathological diagnosis and there is no way I can exclude it on clinical grounds. However, it would be unusual for this to develop while the child was on maximal doses of steroids. The other causes of parenchymal involvement in such a patient are alveolar hemorrhage and vasculitis, none of which can be diagnosed on the basis of the data available.

My final diagnosis would, therefore, be SLE with diffuse proliferative lupus nephritis, lupus encephalopathy, myocarditis with ?pericarditis and ?endocarditis, congestive heart failure, pulmonary edema, anemia, lymphopenia, thrombocytopenia and stress bleeds. The cause of death was myocarditis.

Clinical Discussion

Prof. S.D. Deodhar (Chairman): The case is now open for comments. I would first

invite comments from the treating unit.

Prof. L. Kumar: I would agree with the possibilities suggested by the chief discussant. Myocarditis in this child was an unusual finding and we have not seen such involvement in any of our previous cases of lupus nephritis.

Prof. K.S. Chugh: I agree with the line of reasoning given by Dr. Surjit Singh. However, I think the renal lesion in this child is probably more consistent with a diagnosis of membrano-proliferative lupus nephritis.

Dr. A. Grover: I don't think that this child had viral myocarditis as there was no evidence on ECG. Poor contractility on echocardiography was probably due to SLE myocarditis *per se*.

Dr. D. Kama: The damage due to viral myocarditis is immune mediated and is usually seen in patients with normal immunity. This child was on immuno-suppression; therefore, it would be unlikely that she would have progressive myocardial disease.

Dr. H. Bali: I also do not think that this child had viral myocarditis. The cause of heart failure is probably the primary disease itself.

Prof. R.P. Sapru: A comment was made that myocardial damage in viral myocarditis occurs only in patients with normal immunity. This is not true as disease progression can occur even in patients who are on immuno-suppression. There are many different mechanisms by which a viral infection can result in myocardial damage.

Dr. S. Jain: It is interesting that this child deteriorated in spite of such heavy immuno-suppression. Perhaps the only thing which could have saved her was plasmapheresis.

Dr. I.M.S. Sawhney: As far as the CNS

symptomatology is concerned, I think a possibility of bacterial endocarditis should be kept as it can mimic most of the findings present in this child.

Pathology Protocol by Dr. B. Radotra (PM No. 14981)

This patient had classical lesions of SLE and there is a very good clinicopathological correlation. During life, LE cell test was demonstrated to be positive and therefore, I would like to start by showing LE cell preparation. It showed characteristic homogenous inclusions surrounded by deformed polymorphonuclear leukocytes (*Fig. 2*).

A complete autopsy was performed. On opening the peritoneal cavity there was 250 ml of brown colored fluid. There was no excess fluid in other serous cavities. The kidney lesions were typical and therefore, I would show kidney pathology first.

Kidneys: The right and left kidneys weighed 90 g and 100 g, respectively. The capsule could be easily stripped off. On cut section, the cortex was pale whereas the medulla was congested. Histologically the glomeruli were predominantly affected showing varying morphology. Focal and segmental proliferative lesions were observed (*Fig. 2*) which involved approximately 70-80% glomeruli. Tuft necrosis, kerryorhexis and fibrinoid necrosis were seen in many glomeruli. Some glomeruli also revealed segmental sclerosis and synechia formation. Occasional glomerulus showed hyaline thrombi (*Fig. 3*). Minimal tubular atrophy and chronic interstitial inflammation were seen in focal areas. There was no evidence of vasculitis or renal vein thrombosis; however, occasional fibrin thrombi were noticed in small vessels. Focal and segmental proliferative lesions correspond to Class III lesions; however, since more than 50% glomeruli were involved in this

case such lesions would fall in class IV according to the proposed WHO classification of renal lesions in SLE(6).

On electron microscopy, extensive small discrete to large copious mesangial and subendothelial electron dense deposits were noticed. Many of them revealed organized finger print pattern which is classical for SLE (*Fig. 4*). Immunostaining using antibodies against IgG, IgM, IgA and complement demonstrated positive reaction in the mesangium by indirect immunoperoxidase method (*Fig. 5*).

Heart: The heart weighed 180 g. There was fibrinous pericarditis (*Fig. 6*) on opening; the left ventricle was dilated and showed patchy myocardial dullness. The heart valves were normal. Histological examination revealed focal collection of lymphomononuclear cells. There was evidence of myofiber necrosis (*Fig. 7*). Interstitial edema and occasional vascular hyaline thrombi were present. Focal areas also showed fibrinoid necrosis in subendocardial locations (*Fig. 8*).

Lungs: The right and left lungs weighed 550 altogether. Externally pleuritis was noticed and the lungs were firm to feel. On sectioning, the lower lobes of both lungs were consolidated and hemorrhagic. On microscopic examination there were alveolar hemorrhages and patches of bronchopneumonia. The other areas revealed edema fluid and alveolar macrophages. There was no vasculitis.

Liver: It weighed 900 g and showed fatty change.

Spleen: The spleen weighed 60 g. It revealed perisplenitis and marked congestion. Periarteriolar concentric fibrosis (onion-skinning of penicillary artery) was present (*Fig. 9*).

Gastrointestinal tract: Apart from a 2 cm

mucosal ulceration in the lower esophagus, there was no significant pathology on gross examination of gastrointestinal tract. However, on histological examination, organizing serositis was observed in many areas.

Brain: The brain weighed 1025 g. There was mild cerebral edema and vascular congestion. Histologically hypoxic neuronal damage was noticed (*Fig. 10*), but there was no evidence of vasculitis. Examination of the skeletal nuclei did not show any significant abnormality.

The other organs including pancreas, gall bladder, adrenals and bone marrow did not show significant pathology.

Postmortem Investigations

The postmortem blood showed ANF +++++ (lupus pattern) and strong positivity of anti ds DNA antibodies with values of 1531 IU/ml. The values of negative and positive controls were 171 IU/ml and 1150 IU/ml, respectively. Postmortem blood and ascitic fluid culture did not reveal growth of any microorganisms.

Final Autopsy Diagnosis

Systemic lupus erythematosus (SLE) with

- Lupus nephritis, Class IV
- Serositis
- Myocarditis
- Periarteriolar concentric fibrosis in spleen

Bronchopneumonia

Hypoxic changes and edema-brain

Final Discussion

Prof. S.D. Deodhar: Dr. Radotra where would you put pulmonary lesions? Is it part of pulmonary edema or lupus pneumonia?

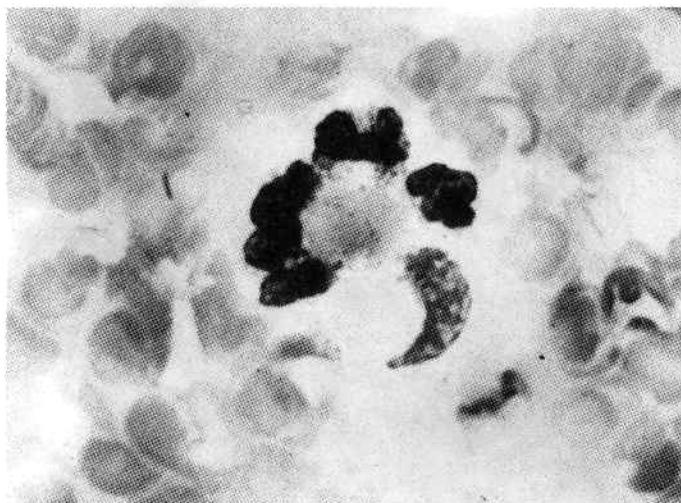


Fig. 1. LE cell showing a homogenous inclusion engulfed by distorted polymorphonuclear leukocytes (Giemsa $\times 1375$).

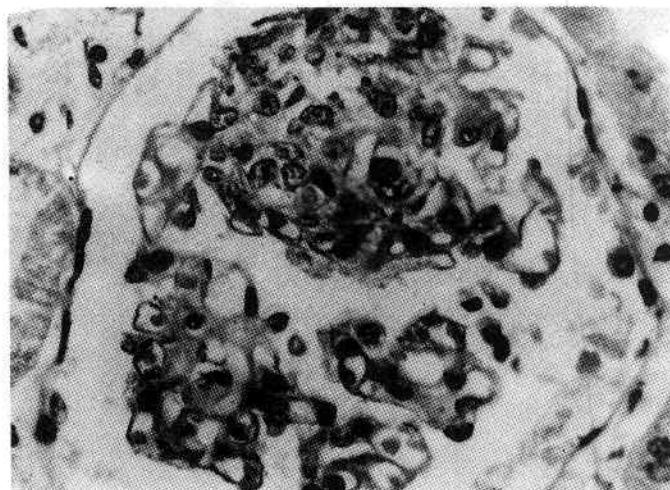


Fig. 2. Segmental proliferation in a glomerular tuft (H&E $\times 550$).

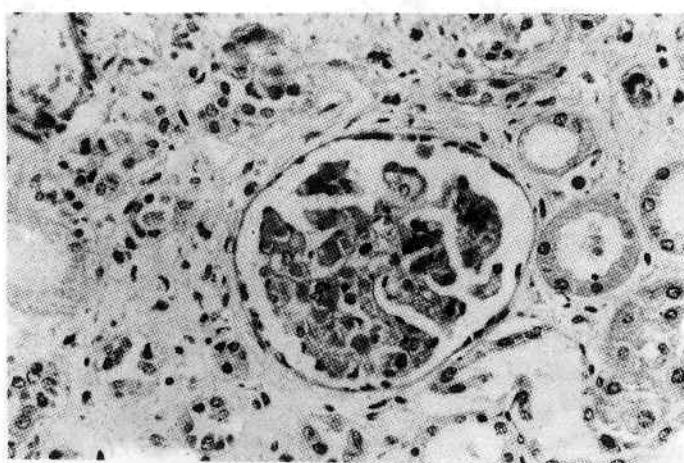


Fig. 3. A glomerulus showing many hyaline thrombi (H&E $\times 140$).

Fig. 4a. Electron micrograph of renal capillary loop showing many electron dense deposits in mesangium and subendothelial location. Some are showing characteristic finger print pattern ($\times 20,000$).

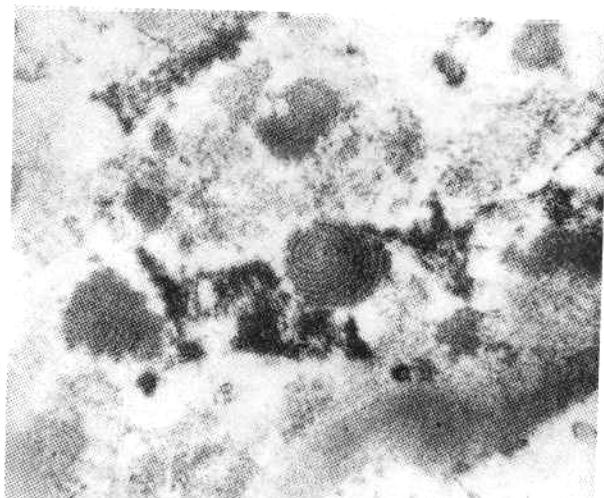
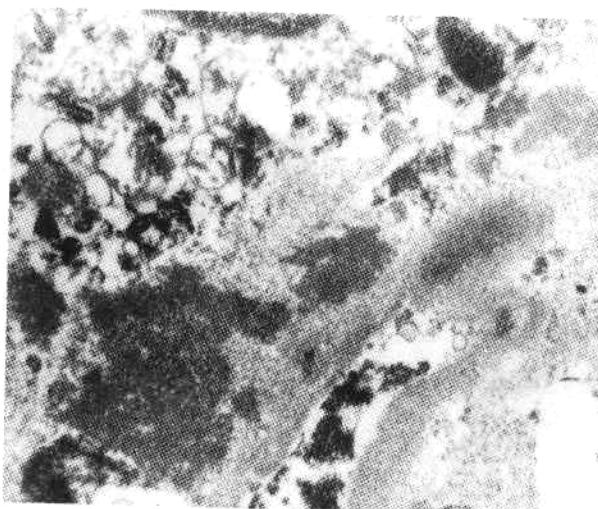


Fig. 4b. Same as figure, 4a in a higher magnification ($\times 30000$).

Fig. 5. Immunostaining showing IgG deposits in the glomeruli ($\times 550$).

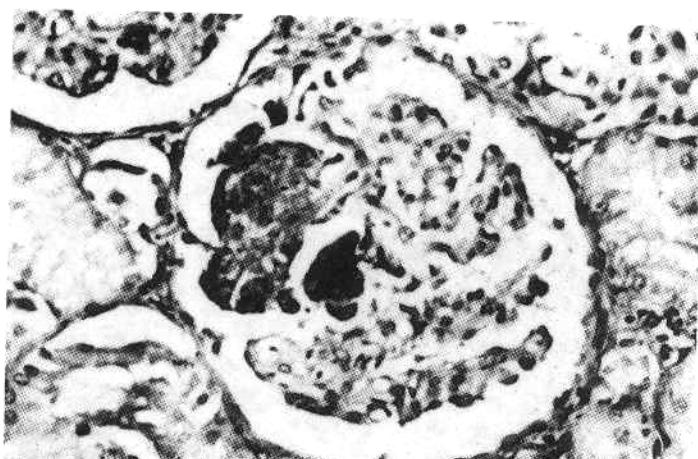


Fig. 6. Fibrinous pericarditis showing shaggy appearance of the heart.

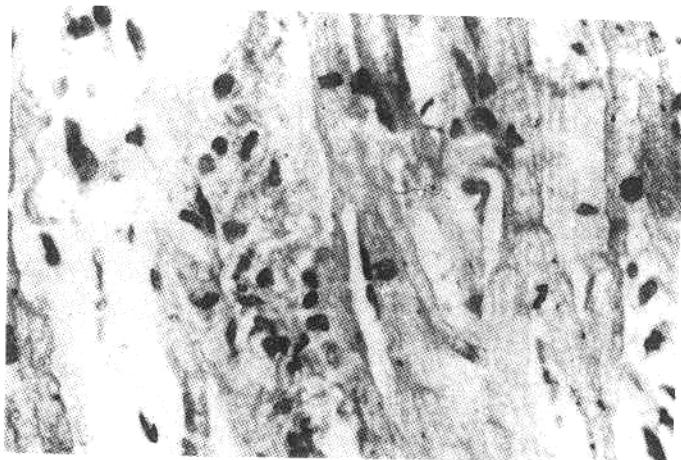
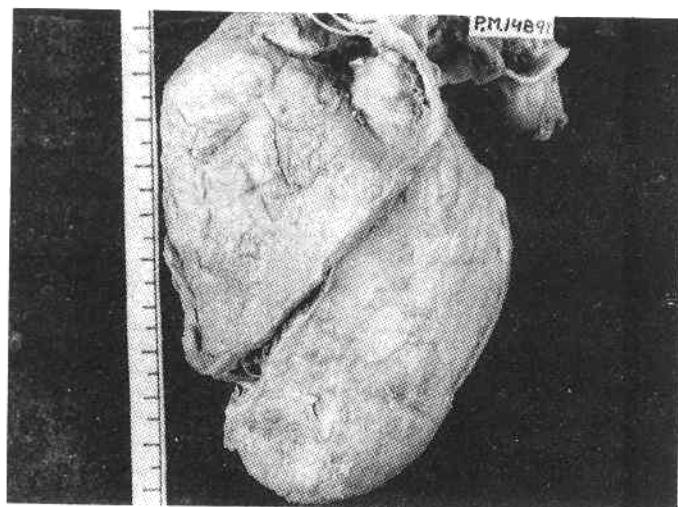


Fig. 7. Microphotograph showing myofibre necrosis (H&E $\times 550$).

Fig. 8. Focal areas of fibrinoid necrosis in subendocardium (H&E $\times 140$).

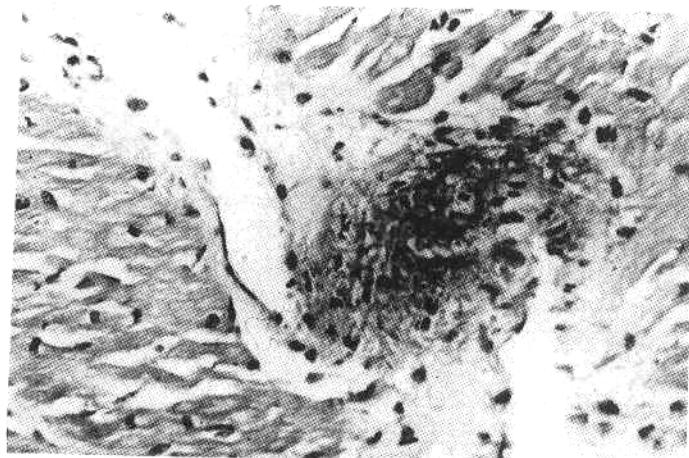


Fig. 9. Concentric periarteriolar fibrosis in the spleen (H&E $\times 140$).

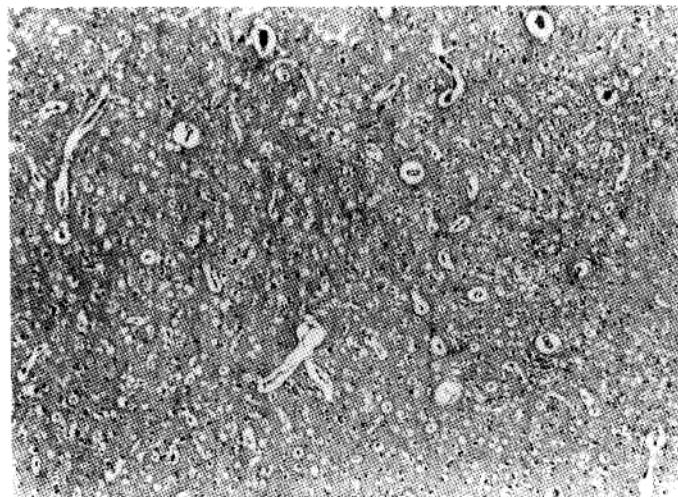
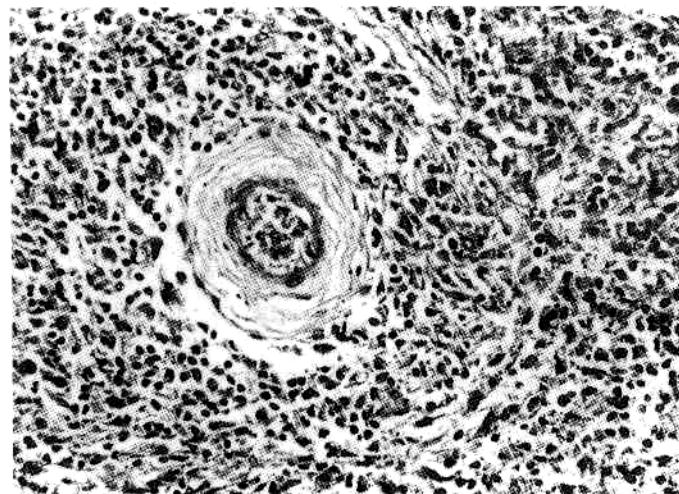


Fig. 10. Microphotograph of cerebral cortex showing hypoxic changes in the neurons.

Dr. B. Radotra: I would think that the alveolar hemorrhages are a part of pulmonary edema. It is not a pulmonary involvement of SLE.

Prof. S.D. Deodhar: There is no evidence of endocarditis although myocarditis and pericarditis have been demonstrated. There is no evidence of virus or virus related manifestations. One of the catches is that most of the studies have shown that after aggressive treatment it takes around 1-2 weeks to have significant changes and treatment with methylprednisolone for 3

days may not have been enough to reverse any of the changes.

Prof. R.P. Sapru: How extensive were the myocardial changes?

Dr. B. Radotra: The lymphocytic infiltrate was seen in all the areas of myocardium examined histopathologically; however, collections of lymphocytes forming dense aggregates were focal in nature.

Prof. R.P. Sapru: The impression that I got was that the pathological changes shown did not explain the severity of the

myocardial dysfunction that was presented clinically. Perhaps the volume overload due to steroids and due to pericardial effusion contributed to the status of this patient. The hypertension commonly seen in this disease has not been recorded in this case and we do not have structural correlates of hypertension to explain it although she had left ventricular enlargement. The other point that viral involvement of myocardium is mainly an immune response is not totally correct, although if you expose this patient to immuno-suppressive therapy viral replication does increase and can aggravate myocardial damage.

Prof. S.D. Deodhar: Prof. Sapru are you suggesting that myocardial involvement could be due to a virus in this case?

Prof. R.P. Sapru: I am not suggesting this view in this particular case. I am clarifying the statement previously made that all viral myocarditis damage is immune mediated.

Dr. A. Grover. The extent of structural changes demonstrated by Dr. Radotra do not explain the degree of failure which this patient had, *i.e.*, the ejection fraction of 18% and obviously the demise of the patient. So the suggestion made earlier before pathology presentation that most of the functional changes of congestive heart failure are immune related in presence of systemic lupus erythematosus is right. It behaves something like cardiac rejection seen in cardiac transplant patients where factors like interleukin I, tumour necrosis factor and protein G contribute to neutralizing adenyl cyclase mechanism which results in energy depletion state in the heart and failure to contract and that is probably what was happening here because we do not have enough structural changes.

Dr. S. Jain: I would like to say that the improvement in the renal function in this patient is due to the improvement in the interstitium because methyl-prednisolone

reduces the interstitial edema and the inflammatory infiltrate. Plasmapheresis is the other mode of therapy in such cases but I am not sure whether it would have helped in this patient.

Dr. S. Singh: There are case reports of SLE presenting with myocarditis and most of these have responded dramatically to oral prednisolone. This child was on maximal immuno-suppression at the time when myocarditis was on but unfortunately did not respond. This is somewhat unusual but I am sure it can occur.

Dr. B. Radotra: I would like to clarify that the myocardial involvement is due to the disease itself and this is a case of SLE myocarditis. There is evidence in the form of foci of fibrinoid necrosis, extensive interstitial edema, hyaline vascular thrombi and focal myofibre necrosis associated with lymphocyte infiltrate.

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