Clinicopathological Conference Report

Lupus Flare in Pregnancy

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CASE REPORT

A 23-year-old primigravida presented to the obstetric department following a referral from Yamunanagar, in view of systemic lupus erythematosus flare. The lady was married for 6 months and following a spontaneous conception, was into her 17th week of twin gestation. Obstetric ultrasonography had confirmed the presence of diamniotic dichorionic twin gestation. The pregnancy was supervised at a private hospital at Yamunanagar. She presently complained of bilateral pedal edema, arthralgia, on-and-off fever with alopecia and rash for 8 weeks. She also gave a history of vulval swelling and difficulty in passing urine for the past 15 days. She photosensitivity and malar rash since childhood. Prior to her admission, she was evaluated at a private hospital and diagnosed to have an underlying systemic lupus erythematosus based on history, clinical features, and laboratory results.

EXAMINATION

At admission the lady was found to be afebrile, having a pulse rate of 76 per minute, blood pressure of 120/80 mm of mercury and oxygen saturation of 92% at room air. Per abdominal examination revealed an 18-week relaxed uterus. Examination of the other systems did not reveal

any abnormality. The arterial blood gas analysis was suggestive of respiratory alkalosis.

Investigations Tables 1 and 2

- *Anti double-stranded DNA (Anti-ds DNA):* >1000 IU/mL
- *Complement protein 4:* <8 mg/dL
- *Complement protein 3:* <15 mg/dL
- *Lupus anticoagulant:* Present
- *Anti-phospholipid antibody (APLA)(IgG):* Present
- *Anti-cardiolipin antibody (ACLA) (IgM):* Present
- *Beta 2 Glycoprotein (IgG/IgM):* Present
- *Anti Ro antibody:* Present
- *HIV:* Negative
- *HBsAg:* Negative
- *HCV:* Negative
- *PT/APTT/PTI:* 14/29/93 seconds
- *24-hour urine protein:* 220 mg/day
- *ECG:* Within normal limits
- *Echocardiography:* No aortic, mitral or tricuspid regurgitation. Normal right ventricular function. No pulmonary hypertension. Normal left ventricular function. No clot or vegetation seen.

Course and Management

A rheumatology consultation was taken to assess the patient. In view of the underlying systemic lupus erythematosus qualifying for a systemic lupus erythematosus disease activity index (SLEDAI) score of 20 (Table 3),

Table 1: Hemogram

	17 Jul	19 Jul
Hb (mg/dL)	8.8	7.9
TLC (per μ L)	13500	12900
Plts (per μ L)	93000	58000
ESR (mm fall 1 st hour)	103	

Hb: Hemoglobin; TLC: Total leucocyte count;
 Plts: Platelets;
 ESR: Erythrocyte sedimentation rate

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Table 2: Biochemistry

	17 Jul	18 Jul	19 Jul
Urea (mg/dL)	46	44	38
Creatinine (mg/dL)	0.3	0.34	0.3
Bilirubin (mg/dL)	0.6	0.5	0.7
AST (IU/mL)	–	20	–
ALT (IU/mL)	–	17	–
ALP (IU/mL)	–	70	–
Uric acid (mg/dL)	–	2.7	–
LDH (IU/L)	–	412	–
Amylase (IU/L)	–	60	–
Lipase (IU/L)	–	24	–
Na (mmol/L)	144	139	137
K (mmol/L)	3.4	3.07	3.4
Cl (mmol/L)	111	111	107
Albumin (gm/dL)	-	2.3	-

AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; Na: Sodium; K: Potassium; Cl: Chloride

the patient was placed on a regimen of Hydroquinone, prednisolone, aspirin, and low molecular weight heparin. At the end of the first day of admission, her urine output was 1050 mL. The following day her blood pressures increased with recordings in the range of 155/100 mm of mercury, accompanied by shortness of breath and drop-in oxygen saturation to 87% on room air. Chest examination revealed bilateral crepitations. She was managed by labetalol, furosemide and oxygen inhalation (by Ventimask). Her urine output was 650 mL. On the last day, the patient continued to have shortness of breath with worsening of tachycardia and tachypnea culminating in cardiac arrest at 1945 hours. She was revived and placed on mechanical ventilation on SIMV mode along with nor-adrenaline infusion. The endotracheal tube suction yielded pink frothy secretions with a simultaneous drop in oxygen saturation to 68%. Spot Troponins I and T were negative. The patient suffered another cardiac arrest at 2115 hours, from which she was revived, but her saturation continued to be persistently low with bilateral lung fields being full of crepitations. The lady succumbed to the third cardiac arrest at 2200 hours.

Dr. Tulika Gupta: Chest X-ray revealed bilateral mid zonal and peri-hilar homogenous opacities with air bronchogram. The costo-phrenic angles were also indistinct, suggesting mild pleural effusion. There was relative sparing of the apices. The differential diagnosis includes:

- Pulmonary edema
- Diffuse alveolar hemorrhage

CASE ANALYSIS

The basic diagnosis in this index case certainly is systemic lupus erythematosus, as it satisfies more than 4 of the

Table 3: American College of Rheumatology Diagnostic Criteria for Systemic Lupus Erythematosus

Malar rash
Discoid rash
Photosensitivity
Oral ulcers
Arthritis
Serositis
Kidney disorders
Neurologic disorder
Blood disorder
Immunologic disorder
Abnormal antinuclear antibodies

11 enumerated criteria (Table 3) given by the American College of Rheumatology.¹ The patient does not fulfill the criteria for definite Antiphospholipid syndrome, though the laboratory criteria were satisfied. However, it is likely from the clinical history and laboratory parameters that the patient has a basic disease of systemic lupus erythematosus with secondary antiphospholipid syndrome.

The skin manifestations of lupus are several, ranging from malar rash, photosensitivity, alopecia, panniculitis, vasculitis, and bullous lesions.² These patients usually show a positive lupus band test, with a granular positivity along the dermo-epidermal junction for antibodies against IgG, IgM, IgA, and C3.³ The musculoskeletal manifestations are usually in the form of non-erosive arthritis with rare cases culminating in deforming Jaccoud's arthropathy.⁴ Hematological disorders in lupus is common with a wide spectrum of manifestations, which can be as non-specific as cytopenias and as florid as autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura, and myelofibrosis.⁵

Kidney involvement in the diagnosed case of lupus clinically present as nephritic or nephrotic syndrome with active sediments in urine examination. The microscopic changes have been classified under classes I to VI, which reflects to some extent the clinical deterioration in terms of glomerular filtration rate, with the exception of class V.⁶ One of the uncommon causes of renal deterioration in lupus patients is due to thrombotic microangiopathy, which is a micro-occlusive disorder secondary to aggregation of platelets in the micro-circulation.⁷ A common diagnostic dilemma in pregnancy with underlying lupus is between exacerbation of underlying disease or a pre-eclamptic state, considering both presents with hypertension.⁸ However, the presence of decreased complement levels, increase anti-ds DNA titers, active sediments in urine and a dramatic response to steroids is characteristic of an underlying lupus flare.⁸

Pleuro-pulmonary complications in lupus patients may manifest as pleuritis, effusion, diffuse alveolar hemorrhage or pneumonitis. Chronic changes include chronic interstitial lung disease, pulmonary arterial hypertension, and shrinking lung syndrome.⁹ The criteria to guide the clinician to make a diagnosis of diffuse alveolar hemorrhage include patchy ground-glass opacities on high resolution computed tomography, drop in hemoglobin in combination with symptomatology of cough, dyspnea, and hemoptysis.¹⁰ The cause of diffuse alveolar hemorrhage remains an underlying capillaritis in cases of lupus.

All the three layers of the heart are known to be affected in lupus including the coronary arteries, manifesting in the decreasing order of incidence as Libman-Sacks endocarditis, myocarditis, pericarditis, coronary artery disease, congestive cardiac failure, and cardiac tamponade.¹¹

The cause of deterioration in the index case may be either pulmonary or cardiogenic. The cardiogenic causes can be cardiomyopathy, hypertension, coronary artery disease or valvular disease. The pulmonary causes can be acute respiratory distress syndrome, pulmonary thromboembolism or infection.

The effect of active lupus during pregnancy is deleterious and is known to result in a fetal loss in more than one-quarter of pregnancies.¹² This makes active and close management of pregnancies with lupus imperative. Risk factors to alert the clinician include increasing proteinuria, presence of antiphospholipid syndrome, thrombocytopenia, uncontrolled hypertension, active lupus nephritis, increasing serum creatinine more than 2.8 mg/dL, active lupus at conception or first trimester, prior history of pregnancy loss, presence of anti Ro/La antibodies, interstitial lung disease, and pulmonary hypertension.¹³

A possibility of the catastrophic antiphospholipid syndrome (APS) needs to be considered in the index case. Catastrophic APS is defined as the occurrence of multiple simultaneous vascular occlusions in a short span of time. However, all four criteria (Tables 4 and 5) need to be satisfied to make a definitive diagnosis of catastrophic APS.¹⁴

Final Clinical Diagnosis

- Primigravida (17 weeks) with twin pregnancy and hypertension
 - Systemic lupus erythematosus
 - Cutaneous involvement
 - Musculoskeletal involvement
 - Diffuse Alveolar Hemorrhage
 - Lupus nephritis
 - Myocarditis/cardiomyopathy–left ventricular failure
- Secondary anti-phospholipid syndrome
- Catastrophic anti-phospholipid syndrome

Clinical Discussion

- *Prof Savita Kumari:* As the patient was admitted under the gynecology unit. First, I invite comments from the treating unit clinician—Dr Vanita.
- *Prof Vanita Suri:* For the obstetrician the strongest predictor for adverse pregnancy outcome is active SLE at conception. So, from this patients' clinical

Table 4: Criteria for definite diagnosis of antiphospholipid syndrome

<i>Clinical criteria</i>	Vascular thrombosis- arterial, venous or small vessel thrombosis, confirmed by histopathology or imaging
	<i>Pregnancy morbidity:</i>
	<ul style="list-style-type: none"> • Unexplained death beyond 10th week of gestation • Premature birth due to preeclampsia, eclampsia or placental insufficiency • 3 or more unexplained abortions before 10th week of gestation
<i>Laboratory criteria</i>	<ul style="list-style-type: none"> • High titres of IgG and IgM anticardiolipin antibodies • Positive lupus anticoagulant test • IgG and/or IgM positive anti-β2GPI
<i>Definite APS is considered when at least one laboratory and one clinical criteria present</i>	

Table 5: Criteria for definite diagnosis of catastrophic antiphospholipid syndrome

Involvement of three or more organ, systems or tissues
Simultaneous development of manifestations in less than a week
Histopathological confirmation of small vessel occlusion in at least one organ
Laboratory confirmation of the presence of antiphospholipid antibodies

profile, it seems that the patient either had a quiescent disease when she was not pregnant and as soon as the gestation increased, the disease either flared up or got unmasked. The anti-dsDNA titers, anemia, thrombocytopenia, deranged urea/creatinine show that the disease was highly active in this patient. This means that the disease activity was high in this patient with a twin pregnancy. The terminal event in this patient was acute pulmonary edema, which can be clinically classified as cardiogenic or can be non-cardiogenic. I personally feel that this was cardiogenic pulmonary oedemas, which lead to the death of the patient. But the echo findings do not suggest the same. The echo does not mention the ejection fraction of the patient. Secondly, diffuse alveolar hemorrhage, diffuse interstitial pneumonia or bleed cannot be ruled out and is an alternate possibility. Pulmonary thromboembolism, which these patients are predisposed too, can also be a differential diagnosis. But pulmonary thromboembolism leading to acute pulmonary edema—pink frothy sputum, with a normal echo is low on cards. So, I feel, it is cardiomyopathy, secondary to an autoimmune disease in a patient with SLE, or a very early peripartum cardiomyopathy.

- *Prof Savita Kumari:* This patient was also seen by the rheumatology services. So, I request the senior resident, who has seen the patient on-call, to make his comments.
- *Dr Arghya Chattopadhyay:* The day when I saw the patient, she was grossly edematous. Anasarca was there. But there were no active features of myocarditis on that day. The pulse rate was within the normal limits. There was no tachypnea or tachycardia. As I remember, she basically got admitted for severe vulval edema, which was the main indication for admission. But the reports she was carrying was suggestive of active lupus, barring one or two reports. The TLC and ESR were very high, though it can be due to pregnancy. We always keep the possibility of infection in any flare of lupus, because even infections can also precipitate the disease activity. So, we started her on 1 mg/kg of prednisolone for the active disease. We also had a plan for giving higher immunosuppressants awaiting further reports which included echocardiography.

However, the same was not suggestive of myocarditis.

- *Dr. Shefali Sharma:* Actually, myocarditis with a normal echo and in a patient who was de-congested is not a possibility. Even if considered, the patient did not respond to steroids. The way, the patient clinically deteriorated, I feel it goes more in the favor of diffuse alveolar hemorrhage because she was not responding to anything. And although the ET aspirate did not show blood, it might not always be the case.
- *The Prof Savita Kumari:* But this echo was done on 17th, and the deterioration was later on. So, we do not have the echo during that period. And secondly, this was a bedside echo. So, there may be some fallacies associated with it. Could this be pulmonary embolism as there was sudden deterioration? She had mild hypoxia from the very beginning. She had underlying ALPA associated condition, and everything can be explained on that basis. However, myocarditis and DAH still remain as possibilities.
- *Prof. Aman Sharma:* The patient has many predisposing factors for catastrophic ALPA like infections and SLE flare, though there is no tell-tale evidence of hemolytic anemia or any elevated liver enzymes. But that does not rule out the possibility of catastrophic ALPA in this patient. So, with the development of all these symptoms within a week and all the features of the primary diagnosis of SLE, and the involvement of multiple systems strongly suggests the possibility of catastrophic ALPA. In histopathology, we can find micro-thrombi, and this may be the main cause of deterioration in this patient.
- *Prof. Sanjay Jain:* There is no doubt that we are dealing with SLE. The main purpose of the discussion would be to look for type lesions and the extent of lesions. We have known the various varieties of SLE. I believe that the primary pathology in this patient lies in the vasculature. As the senior resident has already mentioned that there is a rapid fall of platelet count. On top of it, there was severe hypertension. If you see clinically, somebody who has got severe vulval edema in early pregnancy, the only cause would be proteinuria. Why there is a mismatch between symptoms and laboratory findings? I believe it could be a laboratory error. And if you ask me, we would see intense vascular pathology in most of the circulation, especially in kidneys, lungs, heart, and liver. However, the liver enzymes are normal but they are reports which are about 36 hours old. This can happen. This patient was double antibody positive for ALPA. So, besides that, there is no reason why a young individual would have vulval edema and coronary artery disease. Infections do not kill a person. You know, the presentation has to be true.

- *Dr. Ankur:* Something against a DAH is that there is a Hb fall of only 0.9 gm and in DAH, we do not see a lot of crepts clinically. We see a lot of other findings, but not crepts. And secondly, even with a preserved EF, it is possible that you may have that in the early phases. It could be myocarditis which is progressing. And there could have been other techniques which could have better delineated it. So, in this patient, we have a renal illness and we have a double ALPA positivity. So even an acute coronary syndrome, with an acute coronary thrombosis which has been reported in ALPA could be a possibility. That can explain the sudden development of heart failure.
- *Dr. Rakesh Pilani:* This is a childhood SLE basically and who has presented with a flare in pregnancy. Because she was symptomatic since childhood, and she has an antiphospholipid syndrome (APLA) in the form of lupus anticoagulant (LA) and anti-cardiolipin antibody. LA has the maximum predisposition to thrombosis. The pre-terminal worsening within a week makes catastrophic ALPA very likely in this patient. I would not consider lupus nephritis class III or class IV, because the renal functions are preserved. Hypertension is a late finding, although not seen previously and the urine protein is not high with urine routine not being available. So, I would consider the predominant manifestation of catastrophic ALPA or ALPA associated antiphospholipid syndrome.
- *Dr. Vignesh:* This patient has all the severe risk factors which could have been present and all the risk factors for catastrophic ALPA. So, I would like to consider that worsening respiratory function was mainly due to pulmonary thromboembolism, with other risk factors associated with APLA. Acute pulmonary edema can occur in acute pulmonary embolism also.
- *Dr. Prague:* As far as I can gather from history. From the cardiological point of view, we are looking at myocarditis or acute coronary syndrome. Given a very short history with 2–3 days of hospital stay, I do not think so myocarditis should not be taken into account and such a rapid deterioration will not happen in a case of giant cell myocarditis which is the worst variety of myocarditis. So, myocarditis is practically out. And echo findings show a normal LV function also suggests that even if there is no myocardial edema if myocarditis has to happen, it can manifest in two ways. Either the LV function drops down very rapidly, but the LV thickness remains preserved. We do not give time for the myocardium to deteriorate or degenerate. So, LV function is preserved, so myocarditis is out. What I can still suggest is that in this case of SLE, there can be spontaneous coronary artery dissection. Ostia dissections, coronary artery dissection or a micro-thromboembolism which can lead to acute coronary syndrome can still be a possibility. But personally, I do not think myocarditis should be taken into account. Acute coronary syndrome as a manifestation of coronary artery dissection can be one of the ways by which acute coronary syndrome can present in these patients.
- *Dr. Saket:* If we look at the blood pressure of this patient, the blood pressure is 120/80 on day one and 155/100 on day 2. So, there is a rise of 35 mm of mercury in one day. So, I do not think myocarditis can lead to such an increase in pressure so that probably is out. To my mind thrombotic microangiopathy is one which can lead to such high blood pressure, over a period of one day.
- *Prof. Sanjay Jain:* I wanted to make a comment. It is like the story of seven blind men, with each person looking at one-one aspect. If you start looking at one component, I could tell you there could be ten differential diagnoses. Unfortunately, we forget the clinical situation. Can somebody talk of vulva edema? When someone talks of no nephropathy, with the creatinine being normal, what is the cause of vulval edema in early pregnancy? We forget that this patient had no breathlessness at presentation. You know that is why I am saying, if you have people looking at one small thing and you try to take your bet on that, it will be fallacious. Medicine is a science where you need to knit together all the signs and symptoms.
- *Dr. Valliyapan:* The way this patient presented, with hypertension and anasarca in a setting with SLE, and looking at the X-ray, sudden development of tachypnea in a setting of thrombocytopenia in a patient who is already on heparin, Diffuse alveolar hemorrhage is a known complication. My first differential will be an alveolar hemorrhage.
- *Prof. Aman Sharma:* For catastrophic antiphospholipid syndrome (CAPS) or no CAPS, we have to see the presence of vulval and pedal edema. We can't say that both lung and cardiac involvement occurred simultaneously so that we are trying to bring in three systems and CAPS. If the edema was there for some time, there might have been some renal involvement and there might be some lung hemorrhage. Sometimes with one gram of hemoglobin loss with rapidly on-coming shadows, we will still have to consider lung hemorrhage. And the systolic dysfunction with on-going hypertension—you know conventional medicine teaching is that you would not have hypertension and systolic dysfunction. When you have myocarditis, rather than the blood pressure going down the blood pressure going up would go against the diagnosis of systolic dysfunction.

- *Prof Savita Kumari:* So, to conclude, we have a patient, who was a primigravida, who definitely had SLE with flare. Possible differential diagnosis being discussed are diffuse alveolar hemorrhage and ALPA; myocarditis being less likely. Another possibility as brought out by the cardiologist is coronary ostial dissection. considered. With this, I invite the pathologist Dr. Manoj for the presentation.

Pathology Findings

A partial autopsy was carried out. The prosecutors noted the deceased to be of moderate build. However, no significant skin lesions were seen at the time of autopsy. The serous cavities yielded 200 ml of straw-colored fluid in each pleural cavity, 100 ml of similar straw-colored fluid in both pericardial and peritoneal cavities, respectively.

- *Kidneys:* Both together weighed 402 gm. The external surface was smooth. The cut surface showed maintained cortico-medullary differentiation with few areas of mild medullary congestion (Figs 1A and B). Microscopy showed the presence of diffuse proliferative glomerular lesions having a membranoproliferative pattern (Fig. 1C). Activity was seen in the form of endocapillary hypercellularity (Fig. 1D) (>50%, score 3), neutrophils/karyorrhexis (25–50%, score 2), hyaline deposits (Fig. 1E) (25–50%, score 2), fibrinoid necrosis (<25%, score 2) and few cellular crescents (Fig. panel 1F) (<25%, score 1). No significant changes in chronicity were seen. There
- was dilation of tubules, with the shedding of lining epithelium and areas of attempt at regeneration indicative of acute tubular necrosis. Interstitial areas showed minimal lymphomononuclear cell infiltrate. The blood vessels did not show any pathology. On direct immunofluorescence, antibodies against IgG, IgA, IgM, C3, C1q, Kappa and Lambda were positive (2+) in the mesangial and subendothelial location. Fibrinogen deposition on immunofluorescence was seen in a few glomeruli which had shown fibrinoid necrosis on light microscopy (Fig. Panel 2). Electron microscopy showed the presence of electron-dense immune complex deposits in a subendothelial and mesangial location. Summarising, the kidneys had immune complex glomerulonephritis (lupus nephritis) with a membranoproliferative pattern and crescents, qualifying for a Class IVA lesions and having a modified NIH activity and chronicity indices of 11/24 and 2/12, respectively.
- *Lungs:* Both lungs were heavy and weighed 1213 gm. The pleura was dull with few fibrin tags. The trachea-bronchial tree was unremarkable. The cut surface of the lungs was boggy to feel with large areas of hemorrhagic consolidation in both lower lobes (Fig. panel 3A). Microscopic examination showed extensive edema fluid within the alveolar spaces (Fig. panel 3B). There was evidence of capillaritis in the form of infiltration by neutrophils and karyorrhectic

Figs 1A to F: Cut surface of right (A) Left kidney; (B) Maintained cortico-medullary differentiation with mild medullary congestion. Microscopy showed diffuse proliferative lesions; (C) Hematoxylin and Eosin stained section, 20x magnification, which had a membranoproliferative pattern with endocapillary hypercellularity; (D) Hematoxylin and Eosin stained section, 400x magnification. Some of the glomeruli showed wire loop lesions; (E) PAS stain, 400x magnification and occasional crescents; (F) Jones stain, 400x magnification)

Fig. 2: Direct immunofluorescence showed bright granular positivity for IgG, IgM, IgA, C3, C1q, Kappa and Lambda in a mesangium and subendothelial regions. Few glomeruli showed positivity for fibrinogen along the capillary loops

debris in interstitial capillary walls (Fig. 3C). The consolidated areas corresponded to the areas of intra-alveolar hemorrhages (Fig. 3D). The adjoining visceral pleura also showed fibrin admixed with moderate mixed inflammatory cell infiltrate indicating pleuritis (Fig. 3E). Immunofluorescence showed positivity for antibodies against fibrinogen along the alveolar capillary walls (Fig. 3F). Literature shows that diffuse alveolar hemorrhage is a catastrophic complication of systemic lupus erythematosus which is seen to complicate 2–5 % of SLE cases. Diffuse alveolar hemorrhage is secondary to neutrophilic capillaritis resulting in the destruction of the alveolar septae. There can also be granular immune complex deposition which can be demonstrated by immunofluorescence as shown in the index case.¹⁵

- **Heart:** Weighed 296 gm. The pericardial surface was grossly unremarkable (Fig. 4A). The right inflow, right outflow, and left outflow tract were grossly normal. However, the posterior mitral leaflet and the adjoining posterior wall of the left atrium showed pale brownish discoloration with roughing of the surface (Fig. 4B). Microscopy showed the mitral valve leaflet and the left atrial endocardium to be infiltration by neutrophils admixed with karyorrhectic debris and fibrin (Fig. 4C). Also noted were collections of foamy macrophages (Fig. 4D). This inflammation was seen to extend deeper to involve the underlying myocardium and visceral pericardium, although this was restricted to the posterior wall of the left atrium (Figs 4E to G).

The heart is frequently involved in SLE with more than 50% prevalence when sensitive methods of cardiovascular investigation are used. All three layers of the heart can be affected with a predilection for the left side of the heart.¹⁶

- **Uterus and adnexa:** Gravid uterus on the cut surface showed the presence of a diamniotic-dichorionic placenta, with areas of infarction (Fig. 5A). Microscopy showed evidence of placental insufficiency in the form of areas of infarction, (Fig. 5B) increased syncytial knots, intra-villous fibrin, and calcification (Figs 5C to E). The maternal aspect of the placenta showed features of decidual vasculopathy in form of intimal proliferation (Fig. 5C) and fibrin thrombi within the arteries. The cut surface of the right ovary showed the presence of two corpus luteal cysts, which was confirmed on microscopy. In SLE, the abnormalities in the placenta are those affecting the vasculature which causes extensive infarction, decidual vasculopathy and thrombi leading to an overall decrease in the placental weight.¹⁷
- **Liver:** Weighed 1326 grams with a smooth capsular surface. Cut surface showed exaggerated mottling (Fig. 6A). However, no focal lesion was seen. Under the microscope, the lobular architecture was maintained (Fig. 6B). The portal radicals within the tracts were dilated and congested. Also noted was the presence of centrilobular sinusoidal dilation.
- **Spleen:** Was heavy weighing 1326 grams, having a smooth capsular surface. The capsular surface was

Figs 3A to F: Gross of the lungs showed dull pleural surface with areas of hemorrhagic consolidation in the lower lobes (A) Microscopy showed presence of areas of pulmonary edema; (B) Hematoxylin and Eosin stained section, 40x magnification) with extensive capillaritis; (C) Hematoxylin and Eosin stained section, 400x magnification). The areas of consolidated showed intra-alveolar haemorrhage; (D) Hematoxylin and Eosin stained section, 40x magnification). The inflammation was extending to involve the visceral pleura; (E) Hematoxylin and Eosin stained section, 200x magnification). (F) Direct immunofluorescence showed granular positivity for fibrinogen along the capillary walls

Figs 4A to G: The gross of the heart appeared unremarkable. (A) The left in-flow tract showed the presence of a brownish roughened area on the posterior wall of the left atrium and extending onto the posterior mitral valve leaflet.; (B) Microscopy showed inflammation of the mitral valve and the adjoining left atrial wall; (C) The inflammation in the valve showed neutrophils and karyorrhectic debris; (D) Hematoxylin and Eosin stained section, 400x magnification). The left atrial endocardium showed organised fibrin with underlying foamy macrophages; (E) PAS stain, 200x magnification. The inflammation was seen to extend to involve the underlying myocardium; (F) Hematoxylin and Eosin stained section, 400x magnification and reaching the pericardium; (G) Hematoxylin and Eosin stained section, 400x magnification)

Figs 5A to E: Cut surface of gravid shows diamniotic dichorionic placenta with areas of discoloration (A) Microscopy showed areas of infarction with underlying fibrin thrombi within the utero-placental vessels; (B) Hematoxylin and Eosin stained section, 100x magnification. The deeper uterine arteries showed intimal proliferation and medial hypertrophy; (C) Elastic van Gieson stained section, 400x magnification). The villi showed the presence of syncytial knots; (D) Hematoxylin and Eosin stained section, 400x magnification with many foci of calcification; (E) Hematoxylin and Eosin stained section, 400x magnification.

smooth and shiny, with a congested cut surface. Microscopy showed congested red pulp with prominent peri-arteriolar concentric fibrosis (Figs 6C to E). These arterial changes can be seen in a variety of conditions from diabetes microangiopathy, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, idiopathic portal hypertension, and systemic lupus erythematosus. This had been postulated to be secondary to insudation of plasma proteins through the damaged arterial wall which elicits a fibrotic reaction.¹⁸

- *Adrenal glands:* Sections from both the adrenal glands showed intra-parenchymal congestion (Fig. 7A). Some of the capsular arteries showed segmental vasculitis in the form of fibrinoid necrosis, infiltration by neutrophils and extravasation of RBCs (Figure Panel 7B). Presence of small and medium vessel vasculitis has been described in systemic lupus erythematosus which is indistinguishable from polyarteritis nodosa, having a prevalence of 11–36 %.¹⁹

The bone marrow examination revealed hypercellular spaces packed with cells of all three lineages, indicating a compensated hematopoiesis (Figs 7C to E). The gross and microscopic examination of the pancreas (Fig. panel 6E), stomach, esophagus, small intestine, large intestine, skin (Fig. panel 7C), skeletal muscle, bladder, lymph nodes and thyroid (Fig. 7D) did not show any significant pathological findings.

Final Autopsy Diagnosis

- Lupus nephritis, class IVA
- Extensive capillaritis, pulmonary edema, intra-alveolar hemorrhage, and pleuritis
- Diamniotic-dichorionic placenta with insufficiency secondary to decidual vasculopathy
- Periadrenal arterial vasculitis
- Focal endocarditis limited extension to the underlying cardiac muscle of the left atrial posterior wall
- Periarteriolar concentric fibrosis in the spleen.

Final Discussion

- *Prof Savita Kumari:* Thank you, Dr Manoj. You have beautifully demonstrated various organs affected by lupus. If we see clinic-pathological co-relation Shefali had kept the possibility of DAH and type IV lupus nephritis, which have been shown. But lots of discussions had occurred on APLA, which has not been demonstrated in the pathology. Now both the protocols are open for discussion.
- *Dr Vivek:* My query is to the pathologist. Please correct me if I am wrong. In the kidney biopsy, there was indirect evidence of a high degree of proteinuria. We could see the vacuolization of tubular epithelial cells. This is relevant in view of the comments that were made during the clinical discussion and the fact Dr Jain put forward that we need to take into

Figs 6A to E: Organ complex comprising of a slice of liver, gall bladder, C-loop of duodenum, pancreas, and slice of the spleen. (A) Microscopy showing maintained the lobular architecture of the liver; (B) Masson trichrome stained section, 40x magnification. Sections from spleen showing the periarteriolar concentric onion-skin type of concentric fibrosis; (C) Hematoxylin and Eosin stained section, 400x magnification; (D) Masson trichrome stained section, 400x magnification. Sections from pancreas showing normal histology; (E) Hematoxylin and Eosin stained section, 40x magnification.

Figs 7A to E: Sections from adrenal gland showing mild congestion. (A) Hematoxylin and Eosin stained section, 20x magnification) The periadrenal capsular artery showing segmental vasculitis; (B) Hematoxylin and Eosin stained section, 400x magnification. Sections from skin and thyroid showing normal histology; (C and D) Hematoxylin and Eosin stained section, 40x magnification. Section from bone marrow showing trilineage hematopoiesis; (E) Hematoxylin and Eosin stained section, 400x magnification

consideration the patients overall clinical context. In the clinical protocol, we have just one value of 24-hour urine protein excretion which is 220 mg. So, if we take it into the complete clinical context, the likelihood of it

being wrong is very high. So that is the most important point I would like to put forward. So, if we had had a urine routine, that would have definitely shown some degree of micro-hematuria or albumin of 1+ or 2+ valve.

- *Prof Savita Kumari*: Microscopic urine examination is very important in such a setting. Mild proteinuria in a setting of hypoalbuminemia with serum albumin being 2.3, some correction has to be made on that note.
- *Dr Rakesh Pilani*: This case shows us that the interpretation of ALPA depends on laboratory standards. And one more thing is that the coagulogram, which was repeatedly normal in this patient. In the presence of normal APTT, LA positivity is doubtful. So, the interpretation of LA and anti-beta 2 is difficult. For ACLA, we are not having the titers. So, these things should be considered when we are interpreting the APLA testing.
- *Prof Savita Kumari*: That is why we repeat it after 12 weeks
- *Dr. Jasmina*: Just to correct the last speakers' statement. I don't think we should always have in LA and APLA a prolonged APTT. That is not true. The DRVVT based APLA positivity does not show us this always. So, please do not go back with that fact. A normal APTT can happen. That is why we use a multitude of tests to detect lupus anticoagulant whenever we evaluate a case. The second thing is that I want to tell you is, please feel free to send us samples of APLA syndrome. We have got a new machine which is able to do the anti-cardiolipin, Beta2 glycoprotein antibodies within a day. So, even in this case, I wish we had a post-mortem sample, even an intra-cardiac serum sample, we could have confirmed. I believe this test was from outside. If we could have confirmed it, we would have added to this presentation.
- *Prof. Sanjay Jain*: Point about the involvement of the heart. If you look at lupus, 80% of the organs may have asymptomatic involvement either on light microscopy, EM or immunofluorescence.
- *Dr Aman Sharma*: The kind of placental involvement with the auto-antibody positivity with the placental thrombosis and all that, this is antiphospholipid syndrome. So, it is not a catastrophic antiphospholipid syndrome, but this is antiphospholipid syndrome.
- *Dr. Manoj*: I would like to take Sir's question. I do agree when I made the final slides, I was contemplating whether I should put it as pancarditis or a localized pancarditis. I do agree that the changes are not florid, but there was definite microscopic involvement of the myocardium and pericardium, especially where we had a brownish discoloration. So, I would like to re-iterate that it was a localized endocarditis which extended up to pericardium thereby being focal pancarditis, rather than a diffuse involvement.
- *Dr Prague*: I would like to agree with Dr. Jain. We can't call it as pancarditis. First of all, the pericardium is not involved so only two layers are involved, i.e., the endocardium and the myocardium. The second thing you have told that it is a patchy involvement. Any disease which has systemic involvement will have some patchy involvement of the heart. Until it has a clinical involvement or clinical significance it should not be called as pancarditis. Second, such type of patchy involvement is seen in systemic lupus erythematosus, and you have actually told it as valvulitis. You have shown that it involves the atrial and ventricular aspect of the mitral valve. If we follow this over a period of time 3 to 6 months, this would have grown into the verrucous type of valvular involvement which happens in SLE. So, clinically this may not have killed the patient, nor would have caused any LV dysfunction or RV dysfunction. As you have shown, none of the other parts of the heart were involved. But, over a period of time, I would have thought that this would have gone onto a valvulitis, which would have given you an SLE type of valvulitis which usually happens.
- *Prof. Kim Vaiphei*: I have not seen the slides, but the slides of the endocardium and myocardium which was shown, I thought it was vasculitis because karyorrhexis is seen. So, there is a localized vasculitis, which has resulted in that kind of inflammation. Definitely, I agree to the senior resident's comment from cardiology. I think there is non-bacterial endocarditis, which is expected in the case of SLE.
- *Prof. Radikha*: I thought we should have more discussion on the findings in the placental pathology. You just casually mentioned about infarct, but what we are interested in is what percentage of the placenta was actually involved by infarction. And you have used the fancy word decidual vasculopathy. But what you showed was fibrin in the larger sized vessels, which were the uteroplacental vessels. So, could you elaborate a little more on that and if there were infarct, what percentage of either of the placenta of twin one or twin two were actually involved. Because these are very interesting findings in the placenta. And placental involvement in SLE is well documented in SLE.
- *Dr. Manoj*: First, I would again like to corroborate as the assumptions seem to have been many. As a pathologist, I have to say or show what I have seen. So, you cannot blame me if I say there is focal pancarditis. If I have seen them under the microscope, it is there. It may appear normal on gross, but I have seen neutrophils infiltrating the pericardium, I cannot assume that the neutrophils were just having a walk in the garden. There were definitely there. I do agree that the heart is not involved entirely, but there is a patchy involvement on microscopy, you have to believe it as it was seen

under the microscope. Now coming to the placenta. In the placenta, I do agree the fibrin thrombi were there in the uteroplacental vessels. But the sections from the deeper vessels did show some amount of intimal proliferation and medial hypertrophy. So, the literature I read, talked about similar changes in the placenta in patients with SLE which is why I have put it forth as decidual vasculopathy. The infarct was minimum, about 20% which was the area I showed as the discolored area on the transverse slices.

- *Dr. Vivek*: You showed vasculitis in the adrenal capsule. Did you do immunofluorescence to see if there was concomitant immune complex deposition in that region?
- *Dr. Manoj*: I am at fault for that. Dr. Ritambhara advised me to do an IF, but it was probably my laziness which prevented me from carrying it out.
- *Prof. Ritambhara*: I have come down to support Manoj for the focal pancarditis. It was in the area where we had a Libman-Sachs sort of a situation, with endocarditis on both the sides and the inflammation extending from that area into the myocardium and reaching up to the pericardium. So in morphological terms, it is pancarditis, which is focal and related to that area only which did not present clinically. This is an autopsy which showed an extension of inflammation. The vasculitis was only seen in the adrenal capsule. The pancreas is a site where we get vasculitis in Lupus cases. We sampled extensively, and it was not there.
- *Prof Savita Kumari*: So, I think we had a good discussion. Thank you, everybody.

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