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A 32-Year-Old Man Presented with Nephrotic Syndrome Due to Systemic Lupus Erythematosus Developed Lupus Cerebritis, Pancytopenia and Renal Failure: The Need for New Biologicals

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ABSTRACT

Case Summary

A 32-year-old man presented with nephrotic syndrome due to membranous nephropathy, secondary to systemic lupus erythematosus (SLE). During intensive immunosuppressive therapy with corticosteroid and cyclophosphamide, the patient developed confusion, fits (lupus cerebritis), pancytopenia and rapidly rising serum creatinine (end stage renal failure). Plasmapheresis and rituximab therapy did not make improvement. Later, the patient had gastro-intestinal bleeding, ARDS secondary to bacterial pneumonia, fits and succumbed. Multiple cerebral hemorrhages, consolidation and bilateral small kidneys were found in autopsy.

KEYWORDS: nephrotic syndrome, membranous nephropathy, SLE, lupus cerebritis, pancytopenia, end stage renal failure

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INTRODUCTION

Nephrotic syndrome includes generalized edema, solid albuminuria, hypercholesteremia and hypoalbuminemia. The underlying cause may be primary glomerulonephritis or secondary to systemic diseases such as diabetes mellitus, connective tissue disorder, drugs (penicillamine), amyloidosis, infections (hepatitis B & C) and lymphoma. Membranous nephropathy may be primary or secondary. If it is primary, serum PLAR2 may be positive and special stain with PLAR2 is seen in histology.

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by having varying clinical presentation, severity, unpredictable course as well as outcomes. The disease results from the interaction of genes, environment, and random effects combined to lead to loss of tolerance to self-antigens and active autoimmunity.

Regarding renal involvement among connective tissue disorders, SLE usually affects kidney in early stage of disease; nearly fifty percent of cases of SLE have renal involvement. Renal manifestation may be the earliest manifestation of SLE even without other evidence of systemic involvement. In rheumatoid arthritis, the renal involvement is usually late; kidney is affected via secondary amyloidosis. In systemic sclerosis, kidney involvement is not common and it is also late manifestation. In MCTD, kidney is rarely involved.

Magro-Checa et al found that high-dose glucocorticoids and intravenous cyclophosphamide were the cornerstone for patients with severe symptoms that are thought to reflect inflammation or an underlying autoimmune process. Rituximab, intravenous immunoglobulins, or plasmapheresis were indicated if response was poor (Magro-Checa et al., 2016) (Fanouriakis et al., 2024). Plasmapheresis and rituximab had beneficial effect in refractory lupus enteritis (Aftab et al., 2022). Generally, glucocorticoids are used as 'bridging therapy' during periods of disease activity. If currently used immunosuppressants did not control lupus cerebritis, lupus nephritis, and autoimmune pancytopenia, biologic agents are indicated (Schober & Dooley, 2016).

Pancytopenia in connective tissue disorders is usually seen in SLE. The frequency of hematological involvement in SLE was reported as variable; it was 20% to 80%. Patients with SLE may have anemia; anemia of chronic disease is the most prevalent type encountered in SLE. Microangiopathic hemolytic anemia, iron deficiency anemia, coomb's positive autoimmune hemolytic anemia, red blood cell aplasia, anemia secondary to chronic renal disease, and pancytopenia are also seen in SLE. Chalayer reported bone marrow fibrosis in patient with SLE having peripheral cytopenias (Chalayer et al., 2014) (Vaishnav et al., 2023).

Lupus cerebritis and neurological manifestation were also commonly seen in SLE. Both brain and peripheral nervous system are involved in SLE; and, psychiatric symptoms are often seen too (Schwartz et al., 2019).

CASE PRESENTATION

The deceased was 32 years old man. His story started in February 2024; generalized oedema and hypertension (150/100 mmHg). He had gradual onset of difficulty in swallowing; atrophic scar over both cheeks, pain in small joints of fingers particularly in proximal interphalangeal joints; pain at finger tips; cold finger tips and telangiectasia over nose. Photo (13 &14) demonstrates them.

He had solid albuminuria; normochromic normocytic anemia (hemoglobin 10.2 gm/dl); normal total WBC count ($6.8X10^9$ /L); normal platelet count ($219X10^9$ /L); hypercholesterolemia (fasting cholesterol 243.5 mg/dl); hypoalbuminemia with reverse albumin and globulin ratio (total protein 53.6 g/l with albumin 15.5 g/l); normal blood urea (15.3 mg/dl); and, normal serum creatinine (0.66 mg/dl). Urine protein creatinine ratio was increased (13.56 mg/mg).

Chest radiograph was normal except faint patchy opacity in right middle zone; kidneys were normal in ultrasound. Echocardiogram revealed mild concentric LVH with mild diastolic dysfunction; normal valves; LVEF was 63%; no clots; no vegetations; and no pericardial effusion. Photo (1) shows chest radiograph.

Then, he had low grade fever and erythematous rash in cheek, nose and palms as seen in photo (13 & 14). He had high CRP (4.277mg/dl); very high ESR (100 mm in 1^{st} hr); normal TWBC count ($6.4X10^9$ /L); normal platelet count ($293X10^9$ /L); and falling hemoglobin (9.2 gm/dl). Tumor markers were normal (AFP,CA19.9 & TPSA); CEA was increased slightly (10.84ng/ml). He was an ex-smoker.

Renal biopsy was compatible with membranous nephropathy. It is shown in photo (8, 9, 10, 11 & 12). Photo (8) revealed diffuse thickening of glomerular basement membrane in H&E stain (10X). Photo (9) showed thickened glomerular basement membrane with mild mesangial expansion in PAS stain (20X). Photo (10) demonstrated mild interstitial fibrosis with rare inflammatory cells between tubules in Trichrome stain (20X). Photo (11) illustrated numerous holes and spikes over glomerular basement membranes indicating membranous nephropathy with Silver stain (20X). Photo (12) highlighted immunofluorescence study done form FFPE tissue; it showed weakly positive fine granular PLA2R staining over glomerular basement membrane (Intensity 1+). ENA profile showed strong positivity in Anti SS-A(+++); Anti Ro 52(+++); Anti RNP/Sm(+++); Anti Scl-70(+++); and weak positivity in Anti SS-B(+) and Anti Sm(+).

Therefore, he was treated as a case of SLE with secondary membranous nephropathy in March 2024. Parenteral methylprednisolone and cyclophosphamide were initiated together with chloroquine, calcium, vitamin D, atorvastatin, diuretics, enalapril and vitamins. Clinical sequence is shown in figure (1) flow sheet.

One week after initiation of steroids, he developed generalized fits. The blood pressure became sky high 220/110 mmHg. The conscious level dropped; Glasgow Coma Scale (GCS) became 8/15 ; SaO2 decreased to 94% on air; pulse rate 60/min. Intravenous diazepan infusion, nitrate infusion, endotracheal tube insertion, Ryle's tube feeding and oxygen therapy were initiated.

CT head (march 2024) revealed multiple subcortical and cortical hypodensities in bilateral cerebellar, occipital regions, left corona radiata, frontal and posterior parietal regions; it was highly suggestive of posterior reversible encephalopathy syndrome (PRES). It is demonstrated in photo (5, 6 & 7). Three serial NECT were illustrated in each photo for comparison.

Meanwhile, total WBC count rose to $17X10^9$ /L (neutrophil leucocytosis); anemia persisted (hemoglobin 11.1 gm/dl); platelets dropped dramatically to $83X10^9$ /L; D-dimer was

high (>10); prothrombin time was marginally raised (13.8 sec); and INR was 1.08 sec. They were suggestive of DIC. In the background of SLE with secondary membranous nephropathy presenting with nephrotic syndrome and sudden onset of neurological manifestations were in favor of thrombotic thrombocytopenic purpura. His ESR (130 mm in 1st hr) and CRP (13.3mg/dl) were increasing too. Moreover, blood urea (49.9) and serum creatinine (1.43) were rising; serum sodium was 134 meq/L and potassium was 2.39 meq/L. The patient was having lupus cerebritis, immune cytopenia and renal crisis in spite of immunosuppressive therapy with parenteral corticosteroids and cyclophosphamide.

The conscious level was more or less the same; GCS was 9T/15 (E-3,V-T,M-6); blood pressure became stable at 120/70 mmHg; pulse rate was 96/min; SaO2 was 100% with ventilator. However, hemoglobin was falling to 6 gm/dl; platelets were falling ($20X10^9$ /L). Therefore, plasmapheresis was initiated in end of March. Blood films showed fragmented RBC; they were demonstrated in photo (3 & 4).

In early April 2024, conscious level improved (GCS 15/15); therefore, he was given oxygen 10L/min with reservoir mask. Plasmapheresis was done 3rd time; six units of FFP was given during plasmapheresis. The condition improved gradually and NECT(Head) recheck was repeated in April 2024. The areas of hypodensities were reduced, suggesting an uncommon presentation of posterior reversible encephalopathy syndrome(PRES). It is demonstrated in photo (5, 6 & 7). Three serial NECT were illustrated in each photo for comparison.

Clinical parameters were improved too; total WBC count was $5.7X10^9$ /L; hemoglobin was 6.4 gm/dl; platelet count was $72X10^9$ /L; ESR dropped to 30 mm in 1st hr; CRP decreased to 6.28 mg/L. Renal function improved; blood urea 41.3 mg/dl; serum creatinine 1.24 mg/dl; serum sodium 144 meq/L and potassium 2.89 meq/L. And he became stable till end of April; CRP reduced (1.472mg/L); ESR remained at 32 mm in 1st hr. Therefore, corticosteroid dose was tailored. The condition was stable in April.

Nonetheless, in early May, fever rose again with recrudescence of inflammatory markers; ESR rose to 70 mm in 1st hr; CRP increased to 10.936mg/L; serum creatinine became 2.34 mg/dl. Blood for hemoglobin became low 9.2 gm/dl; total WBC count dropped to $8.2X10^9$ /L; platelet count was $110X10^9$ /L. Urine for routine examination was normal. Therefore, intensive therapy was reinitiated; intravenous cyclophosphamide and methylprednisolone.

In the end of May, fits, fever and pancytopenia recurred. Peripheral blood film showed few fragmented RBC (<1%) with increased neutrophils and thrombocytopenia. All pointing to autoimmune crisis precipitated by sepsis. And, plasmapheresis was done 4th time. The patient blood pressure became sky high 200/120 mmHg; and, nitrate infusion was given and titrated.

In early June 2024, plasmapheresis was repeated on 1/6/2024 as 5th time. On 3/6/2024, he passed melena stool and blood pressure dropped to 100/60 mmHg with tachycardia (pulse rate 90/min). Therefore, 3 units of fresh whole blood was given. Intravenous Rituximab was initiated on 3/6/2024. Four days later, he became dyspnoeic; total WBC count was very high $23.5X10^9$ /L; hemoglobin dropped to 9.7 gm/dl even after transfusion of 3 units of fresh whole blood; platelets decreased to $53X10^9$ /L up; serum creatinine went up to 3.2 mg/dl; CRP was high 6.2mgdl. His SaO2 reduced to 85% with CPAP. Generalized convulsions were in form of status epilepticus; they were controlled with intravenous midazolam infusion. Portable CXR was compatible with consolidation right lung with ARDS. It is shown in photo (2).

On 8/6/2024(03:00Hr); Two days later, the condition was very poor; unconscious (GCS-8/15; E-4,V-1,M-3); blood pressure rose to 200/120 mmHg; and SVT (pulse rate was 150/min). Therefore, intravenous amiodarone and nitrate were given. It was shortly followed by cardiopulmonary arrest.

Autopsy findings were as follows: (1) hematoma measuring 5 X 3 cm underneath the cerebellum, intracerebral hemorrhages at right parietal lobe and supratentorial and infratentorial hemorrhages; (2) congested veins with marked cerebral oedema; (3) consolidation of right lung with serosanguinous secretions on cut section; (4) hemothorax on both sides; (5) left ventricular hypertrophy in cut section of left ventricle; (6) congested liver; (7) both kidneys were small with thin cortex and indistinct cortico-medullary junction suggestive of chronic glomerulonephritis; (8) septic spleen; and, (9) multiple small gastric erosions with congestion. Photo 13 to 23 have demonstrated autopsy findings.

DISCUSSION

Sytemic lupus erythematosus (SLE) is characterized by multiorgan involvement and the presence of autoantibodies. Clinically, this patient had some features of systemic sclerosis like sclerodactyly, terminal resorption and peak nose; however, having renal manifestation was highly suggestive of SLE. And, dermal atrophy and atrophic scar with some telangiectasia over malar area were favoring the diagnosis of SLE. ENA profile showed strong positivity in Anti SS-A(+++); Anti Ro 52(+++); Anti RNP/Sm(+++); Anti Scl-70(+++); and weak positivity in Anti SS-B(+) and Anti Sm(+). Yoshimi et al pointed out that Anti-Ro/SSA antibodies are among the most frequently detected autoantibodies against extractable nuclear antigens and have been associated with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) (Yoshimi et al., 2012). Renal involvement is seen in half of the cases with SLE. Therefore, having renal involvement and neurological involvement in initial presentation in this patient made the diagnosis of SLE. Interpretation of ENA profile should be always combined with clinical features; one reason for case reporting.

Lupus nephritis (LN) remains the most important predictor of morbidity and mortality for patients with SLE. One contemporary cohort from London pointed out that SLE flare and infection remain the top reasons for hospitalization (Lee et al., 2013). This patient presented with nephrotic syndrome. It may be one form of SLE flare in kidney. This patient presented with nephrotic syndrome and renal biopsy was compatible with membranous nephropathy. Therefore, this case was one example of common manifestation of SLE. Treatment of LN usually involves immunosuppressive therapy, typically with mycophenolate mofetil or cyclophosphamide and with glucocorticoids, although these treatments are not uniformly effective. He was initially treated with corticosteroids and cyclophosphamide which was in line with Euro-lupus guideline (Fanouriakis et al., 2024). Having uncontrollable blood pressure and rapidly rising serum creatinine were indicative of poor response to corticosteroids and cyclophosphamide. Moreover, several cycles of plasmapheresis and rituximab did not reverse lupus nephritis, membranous nephropathy. Furthermore. bilaterally contracted small kidneys in autopsy highlighted that all immunosuppressive therapy (corticosteroids, cyclophosphamide, plasmapheresis and rituximab) could not prevent progress of disease - chronic glomerulonephritis; it indicated the need for newer therapy biologic agents. This is one reason for case reporting from nephrology perspectives. The results from recent clinical trials on epratuzumab, tabalumab, and abatacept on LN should be applied (Schober & Dooley, 2016). Anders et al found that a surge of inflammatory cytokine profiles, for example, interleukins (IL-1, IL-6, IL-17, IL-18), tumor necrotic factor, Th1 and Th2 cytokines played a role in LN (Anders et al., 2020) (Alduraibi & Tsokos, 2024). Several reports mentioned that despite increased knowledge of disease pathogenesis and improved treatment options, LN remains a substantial cause of morbidity and death among patients with SLE.

This patient had severe renal and neurological involvement as well as pancytopenia; clinical deterioration with glucocorticoids, cyclophosphamide. Generally, glucocorticoids are used as 'bridging therapy' during periods of disease activity. Cyclophosphamide and rituximab are recommended in organ-threatening and refractory disease, respectively. According to Magro-Checa et al, high-dose glucocorticoids and intravenous cyclophosphamide remain the cornerstone for patients with severe symptoms that are thought to reflect inflammation or an underlying autoimmune process. Rituximab, intravenous immunoglobulins, or plasmapheresis may be used if response is not achieved (Magro-Checa et al., 2016) (Fanouriakis et al., 2024). Besides, plasmapheresis and rituximab were reported to have a potential role in refractory lupus enteritis (Aftab et al., 2022). However, rituximab and several cycles of plasmapheresis did not make improvement in this case. Therefore, currently used immunosuppressants did not control lupus cerebritis, lupus nephritis, and autoimmune pancytopenia. It again pointed out the role of biologic agents. The affordability of biologic agents in low-income country is another question for us. New agents are in early phase trials (Schober & Dooley, 2016).

Complication of thrombocytopenia led to torrential gastro-intestinal bleeding. Low white cell count could not fight pneumonia and the patient developed ARDS. Finally, the patient had cerebral hemorrhage as a consequence of low platelets. Systemic lupus erythematosus (SLE) often presents with cytopenia(s); however, pancytopenia is found less commonly, requiring the consideration of possible aetiologies other than the primary disease. Around 18% to 80% of patients with SLE suffer from anemia. Anemia of chronic disease is the most prevalent type encountered in SLE. Microangiopathic hemolytic anemia, iron deficiency anemia, coomb's positive autoimmune hemolytic anemia, red blood cell aplasia, anemia secondary to chronic renal disease, and pancytopenia are also seen in SLE. Chalayer reported bone marrow fibrosis in patient with SLE having peripheral cytopenias (Chalayer et al., 2014) (Vaishnav et al., 2023). In this patient, pancytopenia was thought to be due to auto-immune involvement of bone marrow though bone marrow examination was not done. Autoimmune cytopenia is not infrequent in SLE owing to the presence of antigens in the blood vessel compartment, resulting in more production of antibodies (Bashal, 2013). Vaishnav et al found autoimmune myelofibrosis in patient with SLE having pancytopenia (Vaishnav et al., 2023). In treatment-refractory SLE, autologous nonmyeloablative stem cell transplant was suggested to ameliorate disease activity, improvement in serologic markers, and reversal of organ dysfunction (Burt et al., 2006). Having high D dimer level may be related with SLE or nephrotic syndrome in this patient. There was no evidence of thrombosis and anti-phospholipid antibody were negative. Therefore, he was very unlikely to have catastrophic anti-phospholipid syndrome (Gansner & Berliner, 2018) (Tanariyakul et al., 2024). Catastrophic antiphospholipid antibody syndrome (CAPS) and macrophage activation syndrome (MAS) are both life-threatening hematologic disorders that infrequently afflict patients with rheumatologic disease. CAPS is characterized by fulminant multiorgan damage related to small vessel thrombosis in the setting of persistent antiphospholipid antibodies.

The central and peripheral nervous system involvement and psychiatric symptoms are often seen in SLE. Seizures, aseptic meningitis, demyelinating syndrome, and movement disorder are other CNS manifestations (Schwartz et al., 2019). This patient had fits and confusion in early course of disease; and, CT scan head revealed multiple subcortical and cortical hypodensities in bilateral cerebellar, occipital regions, left corona radiata, frontal and posterior parietal regions. They improved over few weeks; it was revealed in serial NECT head. Therefore, both clinical improvement and improvement

in NECT head were suggestive of PRES Syndrome (posterior reversible encephalopathy syndrome(PRES). If a patient had fits, confusion, headache and MRI Brain revealed white matter lesion, the possibilities were as follows: (1) auto-immune encephalitis; (2) infectious encephalitis; (3) paraneoplastic lesions; (4) cerebral venous sinus thrombosis (MR Venogram); (5) acute demyelinating encephalopathy; (6) CNS lymphoma; and (7) acute toxic leukoencephalopathy (Heroin, methamphetamine, benzodiazepine, lead, CO, cranial radiation). The patient again had generalized fits terminally; and, there were several cerebral hemorrhages in autopsy. And, the hemorrhages were results of thrombocytopenia.

This patient did not have COVID-19 infection; he received COVID-19 vaccination a year ago. Rare cases of COVID-19 infection and vaccine-triggered autoimmune diseases were reported by Fekih-Romdhane et al in 2023; they postulated that there might be chronological relationship between COVID-19 infection, vaccination and the first lupus cerebritis (Fekih-Romdhane et al., 2023).

Generally, glucocorticoids are used as 'bridging therapy' during periods of disease activity. Cyclophosphamide and rituximab are recommended in organ-threatening and refractory disease, respectively(Fanouriakis et al., 2024). (2023). This patient had severe renal and neurological involvement as well as pancytopenia; clinical deterioration with glucocorticoids, cyclophosphamide. And rituximab and plasmapheresis did not make improvement. Complication of thrombocytopenia led to torrential gastro-intestinal bleeding. Low white cell count could not fight pneumonia and the patient developed ARDS. Finally, the patient had cerebral hemorrhage as a complication of low platelets. This patient scenario supported that SLE is a chronic systemic autoimmune disease characterized by having varying clinical presentation, severity, unpredictable course as well as outcomes.

Recent disease-modifying conventional and biologic agents have enhanced rates of attaining both short- and long-term management goals, including minimization of glucocorticoid dose and use (El Miedany et al., 2023) (Fanouriakis et al., 2024). Therefore, the treat-to-target management of patients with SLE depended on individual clinical scenarios; it should be based on a combination of evidence and expert opinion. This patient should have received biologic agent and it might change his outcome. In treatment-refractory SLE, autologous nonmyeloablative stem cell transplant was suggested to ameliorate disease activity, improvement in serologic markers, and reversal of organ dysfunction (Burt et al., 2006).

CONCLUSION

SLE is a chronic systemic autoimmune disease characterized by having varying clinical presentation, severity, unpredictable course as well as outcomes. This patient had severe life -threatening manifestations; renal, neurological and hematological involvements. Poor immunity due to SLE itself, corticosteroids and immunosuppressants and leucopenia finally led to severe pneumonia and ARDS. Severe thrombocytopenia due to SLE itself, DIC and immunosuppressants caused fatal cerebral hemorrhages. Recent disease-modifying conventional agents did not prevent severe organ threatening manifestation in this case. If we initiated biologic agents early, the outcome of this patient would have changed.

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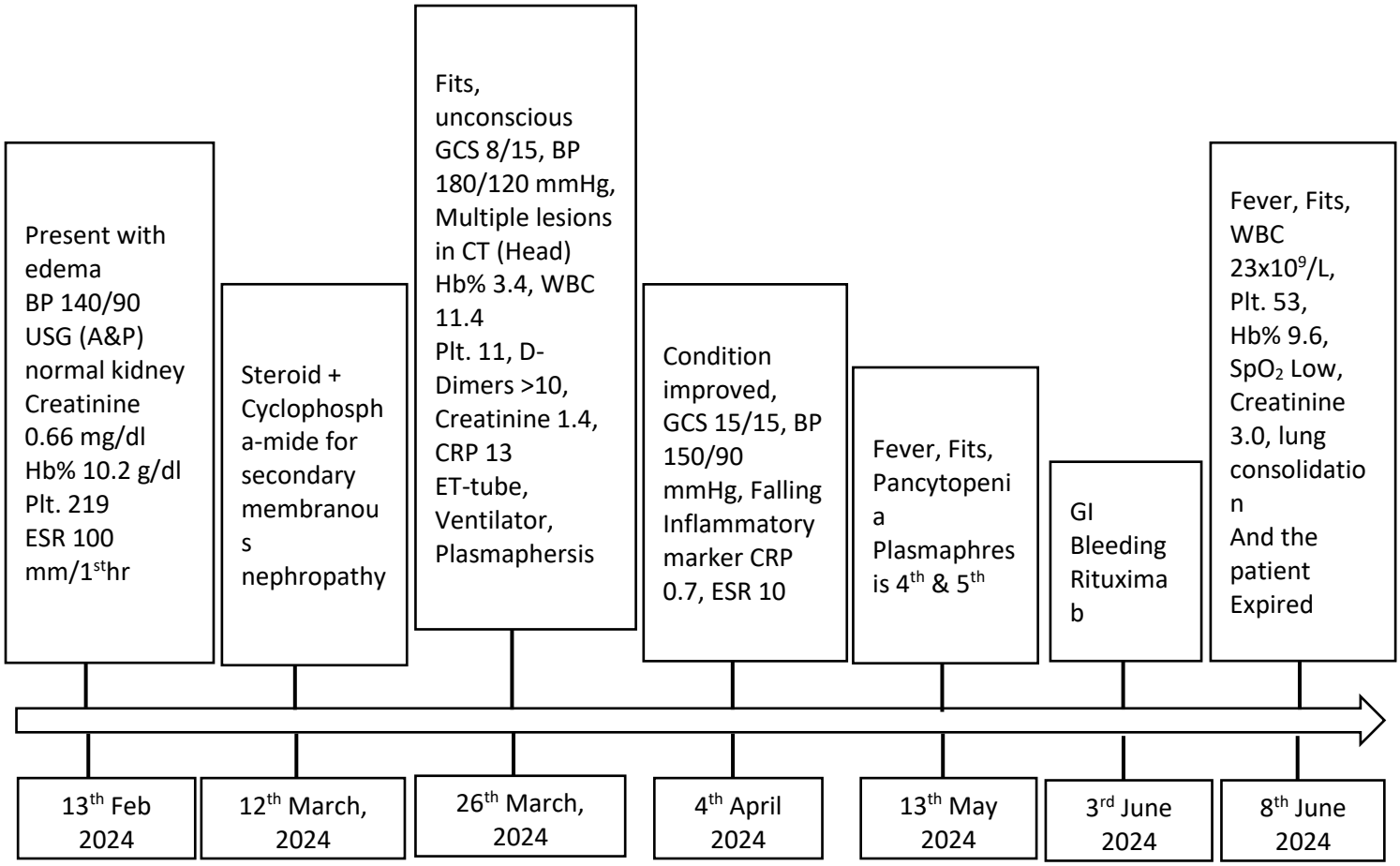

Figure (1) Course of illness in sequence

Table (1) Serial laboratory parameters

Date	13/2	22/2	19/3	22/3	24/3	25/3	27/3	28/3	29/3	30/3	31/3	15/4	26/4	8/5	13/5	23/5	28/5	29/5	3/6	7/6
Hb (g/dl)	10.2	9.2	11	6.7	5.7	5.5	3.4	8.0	8.7	6.8	7.9	6.6	8.6	9.3	9.2	9.8	10.9	10	5.6	9.7
TWBC ($x10^9$/L)	6.8	6.4	17.0	13.3	18.0	24.8	11.4	13.3	19	12.5	9.3	6.2	8.3	7.2	8.2	4.6	7.0	3.0	6.8	23.5
Platelets ($x10^9$/L)	219	293	83	42	38	17	11	27	40	39	33	138	182	100	110	77	30	35	25	53
Urea (mg/dl)	15.3		49.9	71.8	91.8	113	83	66	76	55	47	31.6	35		34		57	68	75	92.3
Creatinine (mg/dl)	0.66		1.4	1.8	1.9	2.2	1.7	1.1	1.2	0.9	0.8	0.9	1.0	1.0	1.3	2.2	1.6	1.6	3.2	3.0
Na (mmol/L)			134	148	142	150	151	142	145	142	142	140	145	141			141	137		147
K (mmol/L)			2.4	3.0	3.2	3.5	3.5	3.4	4	3.1	3.5	4.0	2.7	4.7			3.0	3.6		3.0

Cl (mmol/L)			**93.7**	**106**	**98**	**105**	**113**	**106**	**107**	**107**	**109**	**110**	**103**	**101**			**111**	**108**		**110**
PT (Sec.)	**10.1**		**13.8**																	
INR	**0.72**		**1.6**																	
D-dimer (µg/ml)			**>10**																	
LDH (U/L)			**1075**														**695**			
Cholesterol (mg/dl)	**243**																			
Total protein (g/dl)	**53.6**																			
Albumin (g/dl)	**15.3**																			
Globulin (g/dl)	**38.3**																			
CRP (mg/L)		**4.2**	**13.3**										**0.7**		**10**					**6.2**
ESR		**100**	**130**										**10**		**19**		**10**			
Urine PCR (mg/g)	**13.56**																			
Urine albumin	**solid**																			
PLAR2				**neg**																

Table (1) Serial laboratory parameters

Date	13/2	22/2	19/3	22/3	24/3	25/3	27/3	28/3	29/3	30/3	31/3	15/4	26/4	8/5	13/5	23/5	28/5	29/5	3/6	7/6
Hb (g/dl)	10.2	9.2	11	6.7	5.7	5.5	3.4	8.0	8.7	6.8	7.9	6.6	8.6	9.3	9.2	9.8	10.9	10	5.6	9.7
TWBC ($x10^9$/L)	6.8	6.4	17.0	13.3	18.0	24.8	11.4	13.3	19	12.5	9.3	6.2	8.3	7.2	8.2	4.6	7.0	3.0	6.8	23.5
Platelets ($x10^9$/L)	219	293	83	42	38	17	11	27	40	39	33	138	182	100	110	77	30	35	25	53
Urea (mg/dl)	15.3		49.9	71.8	91.8	113	83	66	76	55	47	31.6	35		34		57	68	75	92.3
Creatinine (mg/dl)	0.66		1.4	1.8	1.9	2.2	1.7	1.1	1.2	0.9	0.8	0.9	1.0	1.0	1.3	2.2	1.6	1.6	3.2	3.0
Na (mmol/L)			134	148	142	150	151	142	145	142	142	140	145	141			141	137		147
K (mmol/L)			2.4	3.0	3.2	3.5	3.5	3.4	4	3.1	3.5	4.0	2.7	4.7			3.0	3.6		3.0
Cl (mmol/L)			93.7	106	98	105	113	106	107	107	109	110	103	101			111	108		110
PT (Sec.)	10.1		13.8																	
INR	0.72		1.6																	
D-dimer (µg/ml)			>10																	
LDH (U/L)			1075														695			
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Globulin (g/dl)	38.3																			
CRP (mg/L)		4.2	13.3										0.7		10					6.2
ESR		100	130										10		19		10			
Urine PCR (mg/g)	13.56																			
Urine albumin	solid																			
PLAR2				neg																

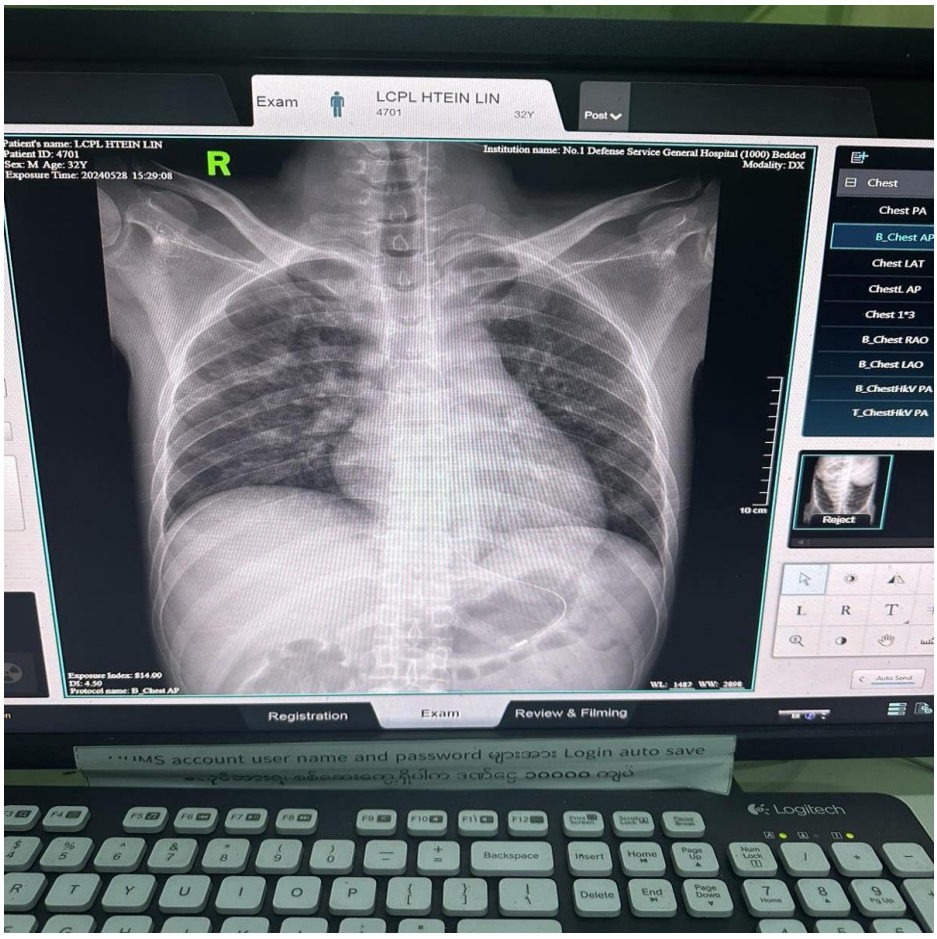


Photo (1) Chest radiograph done in 28th May 2024, showing faint patchy opacities in right middle zone

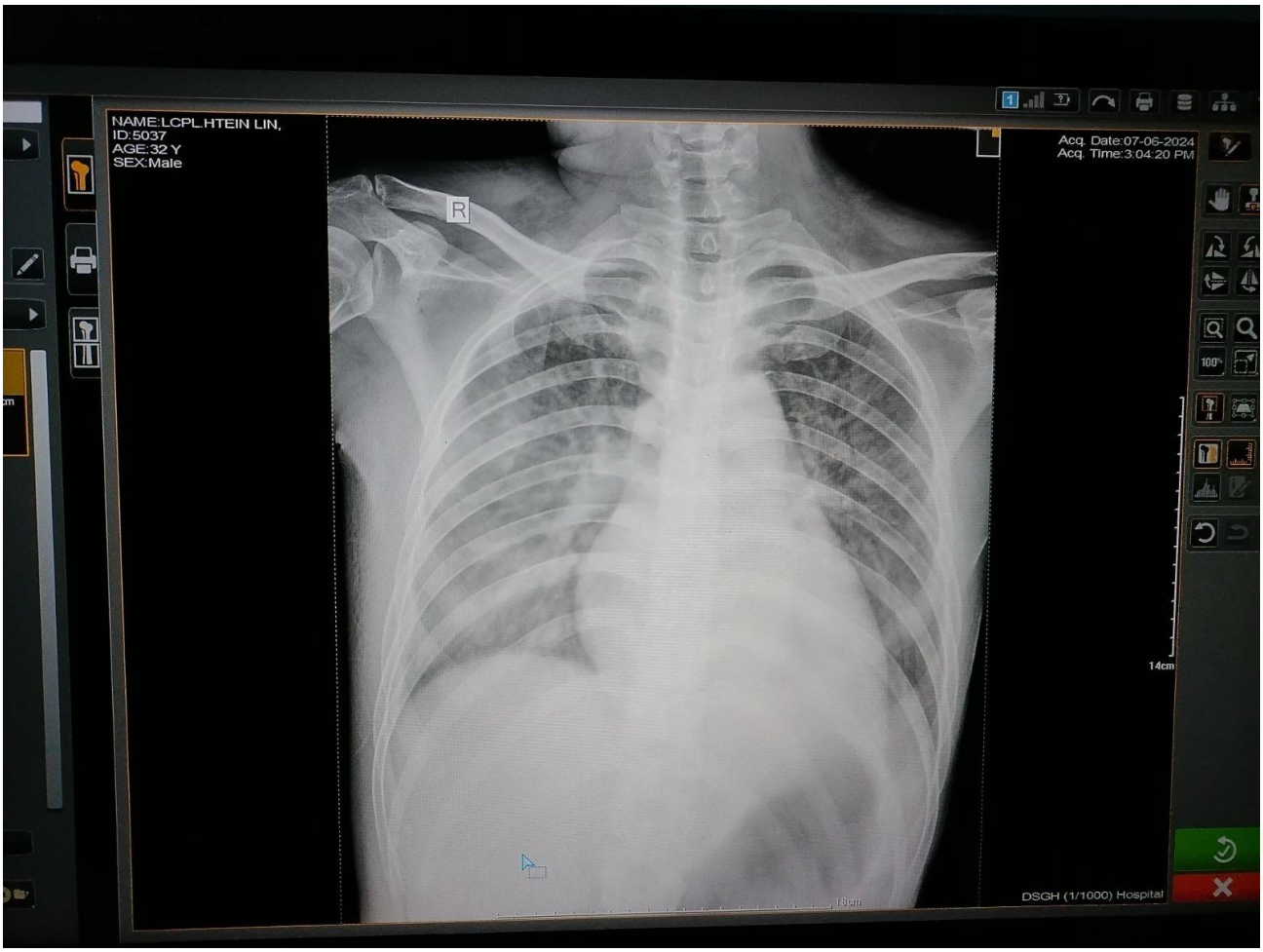


Photo (2) Chest radiograph done in 7th July 2024, showing consolidation in right lung with ARDS

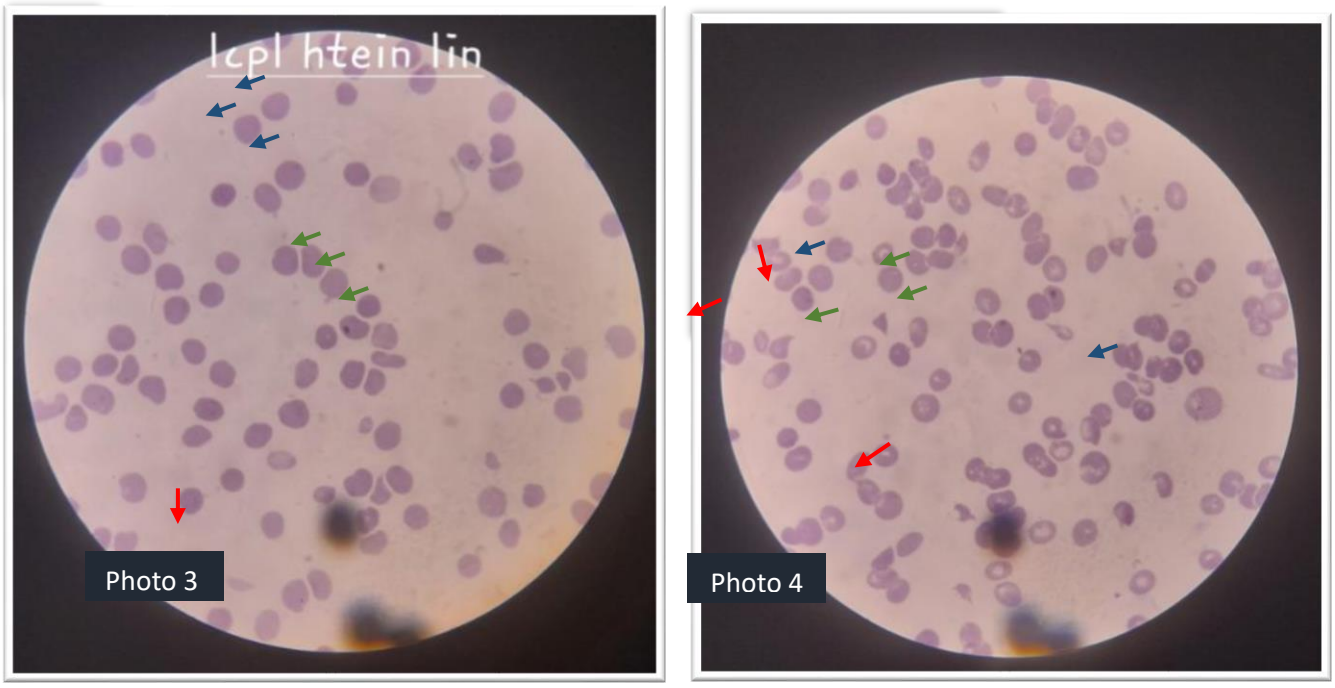
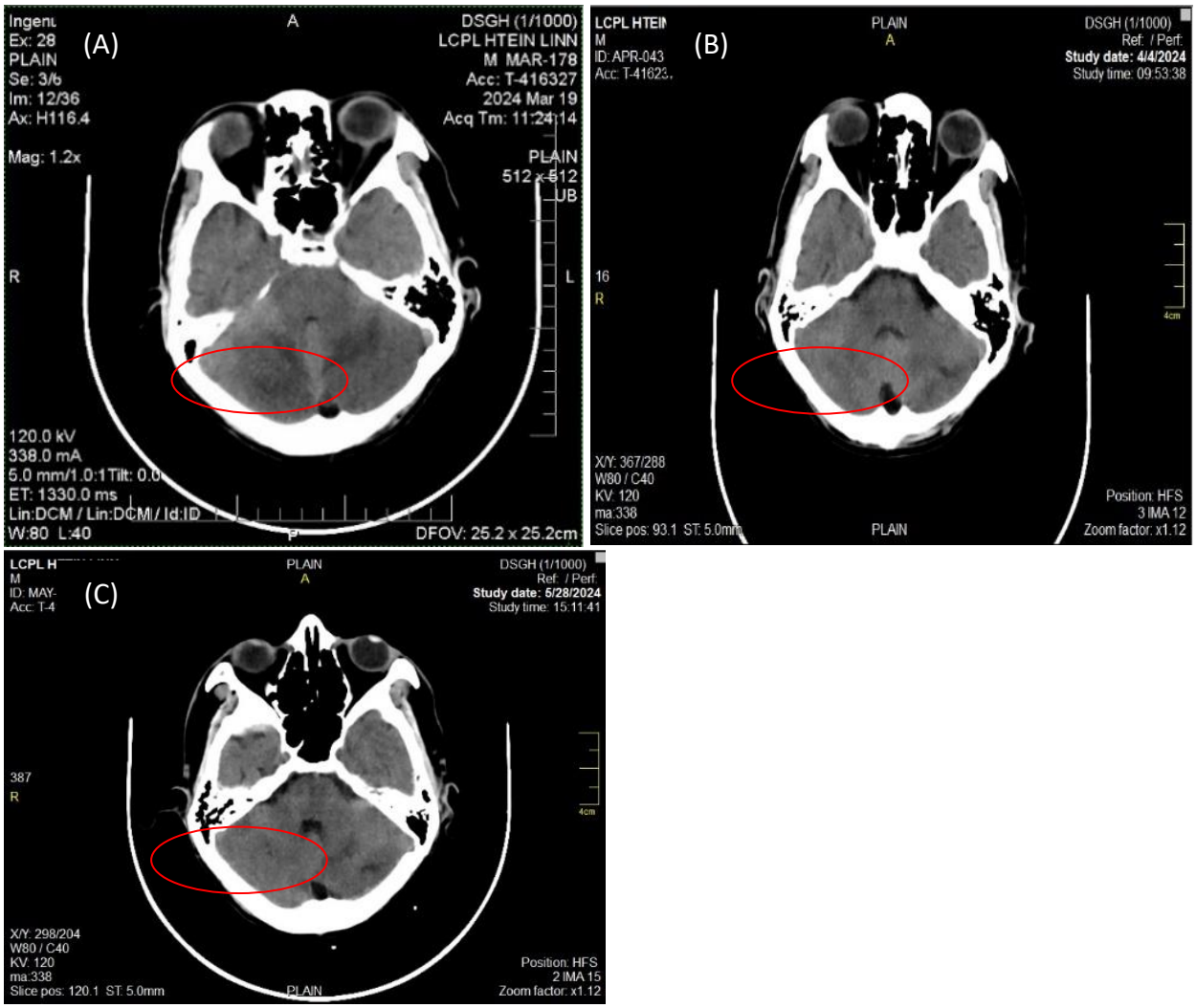
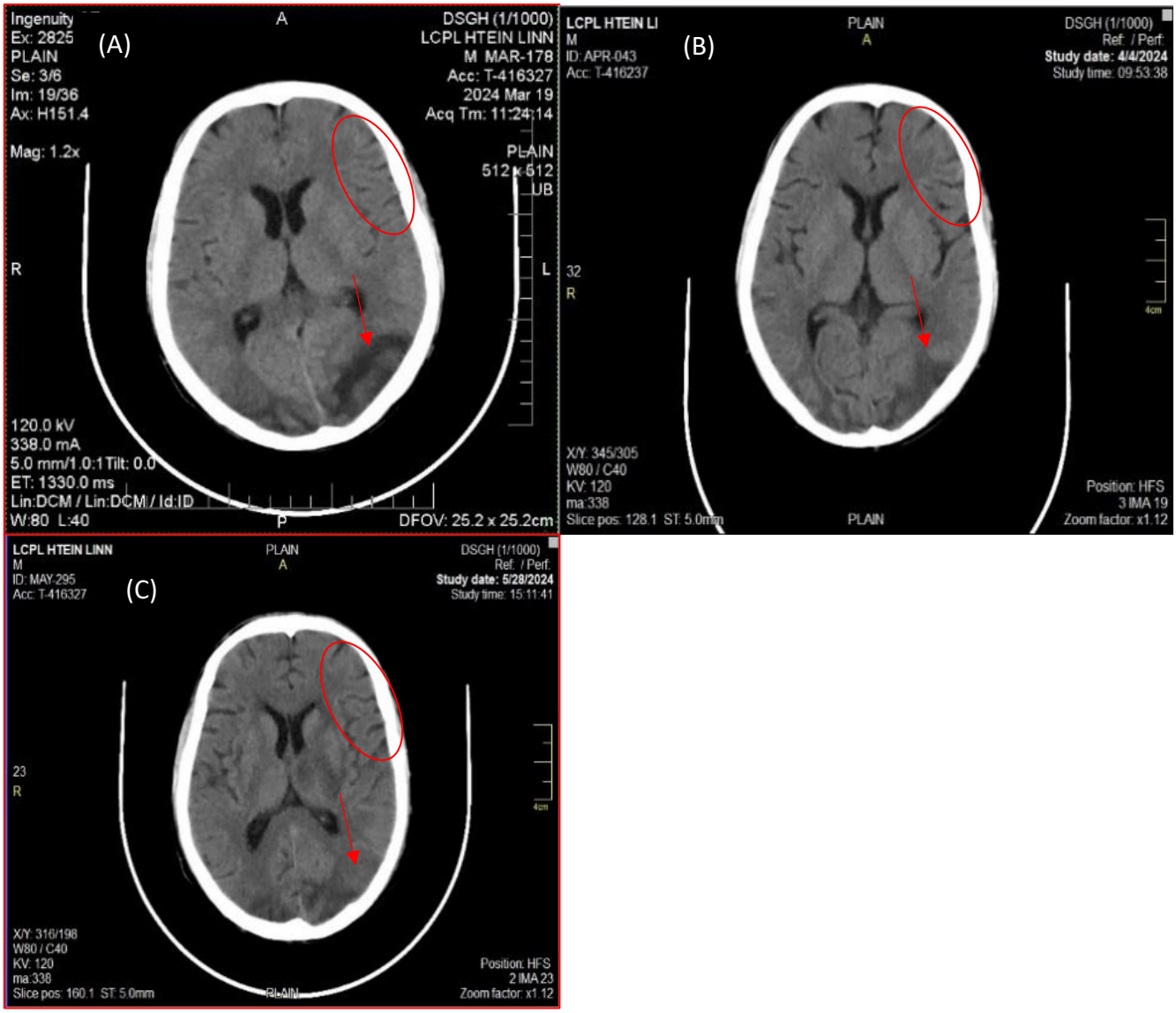


Photo (3 and 4) Peripheral blood film showing spherocytes (blue arrows), some polychromatic cell (green arrows) and few fragmented RBC (red arrows) with low platelet count compatible with immune hemolytic anemia and thrombocytopenia



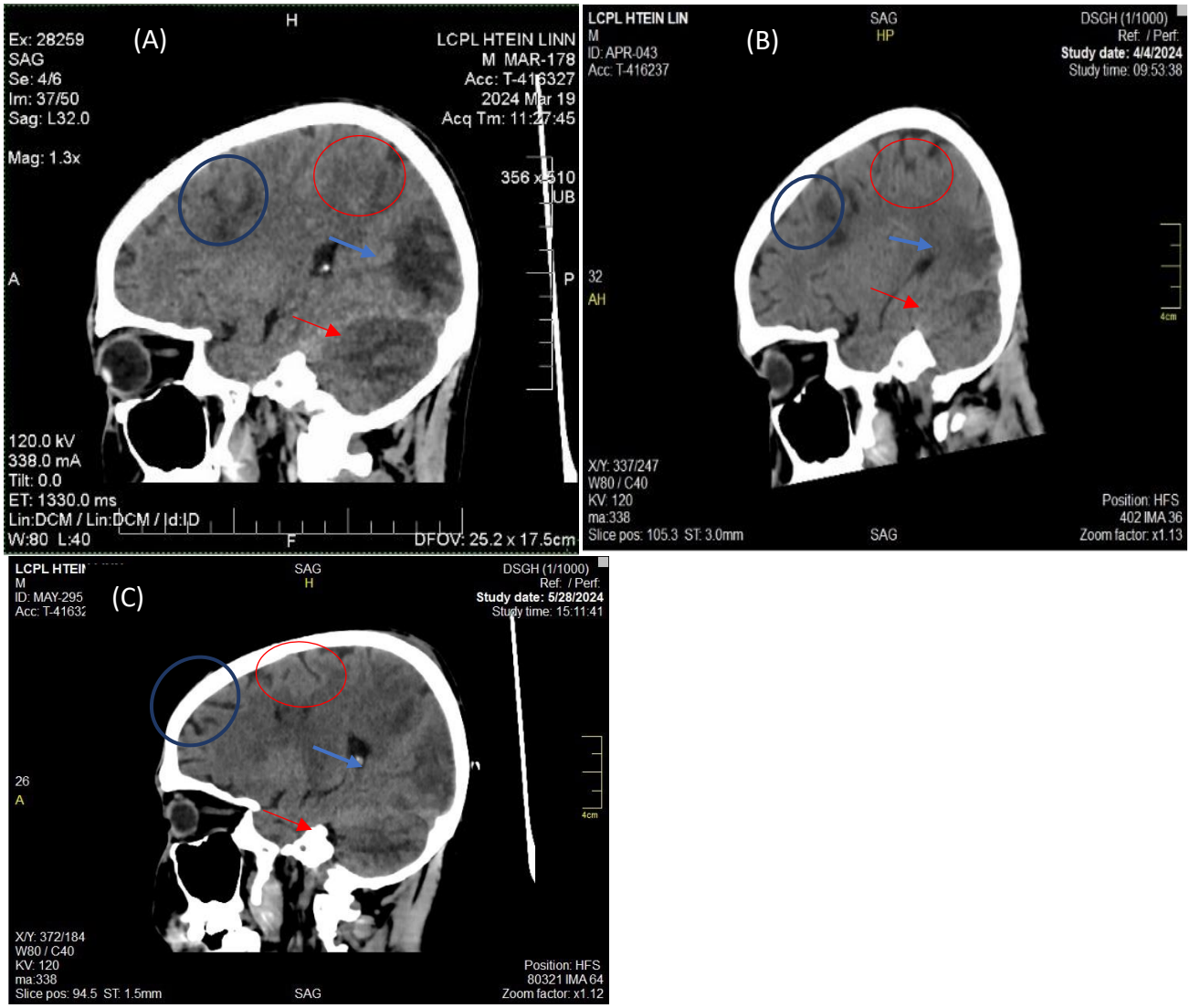
The axial view of serial image of NECT (head) showing a subcortical hypodensities (red circle) at both lobe of cerebellum on 19th March 2024 shown in figure (A) , it was improved in 4th April 2024 Figure (B) and In 28th May 2024 showed reappearance and more severe subcortical and cortical infarct of both cerebellum figure (C)

Photo (5) Comparison of NECT head cerebellum at three different periods (March, April & May)



The axial view of serial image of NECT (head) showing subcortical and cortical hypodensities in occipital regions (Blue arrow), left corona radiata (Red arrow), Frontal and posterior parietal regions (Red circle) and narrowing of sulci and gyri on 19th March 2024 shown in figure (A). It was improving in 4th April 2024 Figure (B). Figure (C) was taken in 28th May 2024.

Photo (6) Comparison of NECT head at three different periods (March, April & May)



The sagittal view of serial image of NECT (head) showing subcortical and cortical hypodensities in occipital regions (Blue arrow), cerebellum red (arrow), Frontal (Blue circle) and posterior parietal regions (Red circle) and narrowing of sulci and gyri on 19th March 2024 shown in figure (A). It was improving in 4th April 2024 Figure (B). Figure (C) was taken in 28th May 2024.

Photo (7) Comparison of NECT head sagittal view at three different periods (March, April & May)

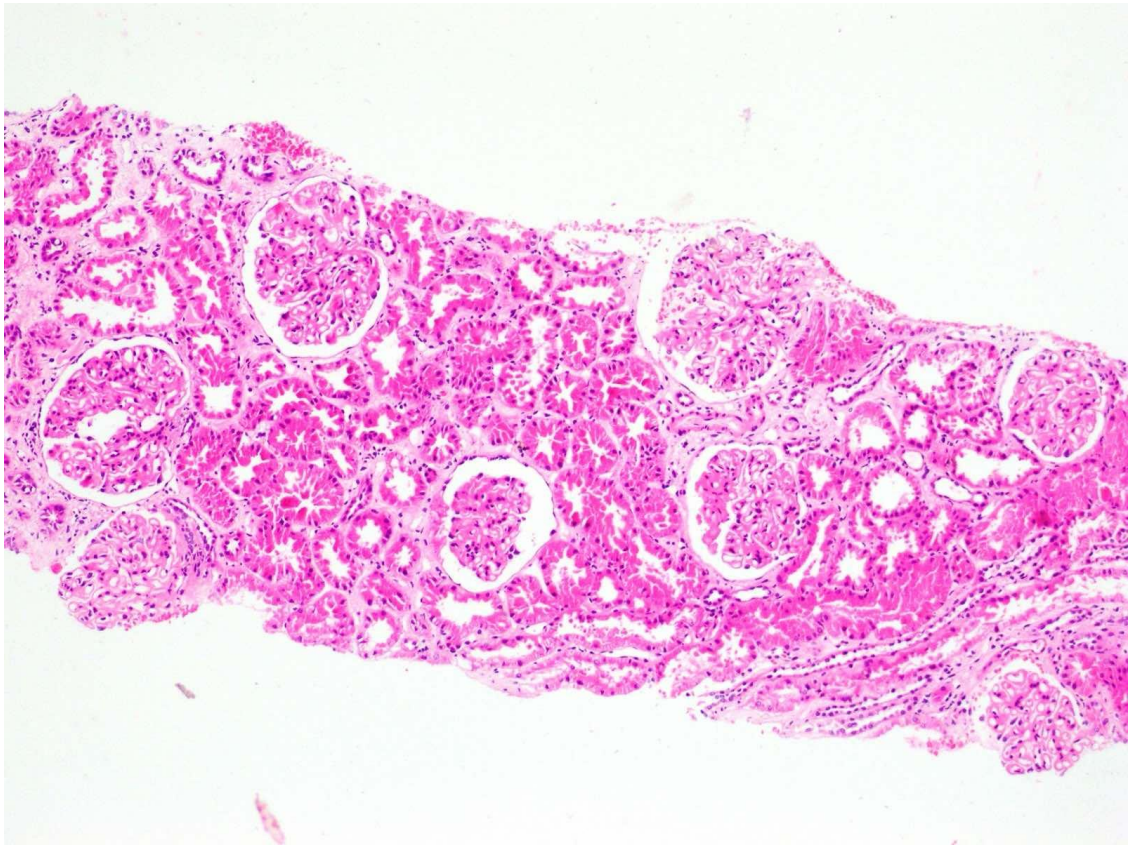


Photo (8) Almost all glomeruli with diffuse thickening of glomerular basement membrane (H&E stain 10X)

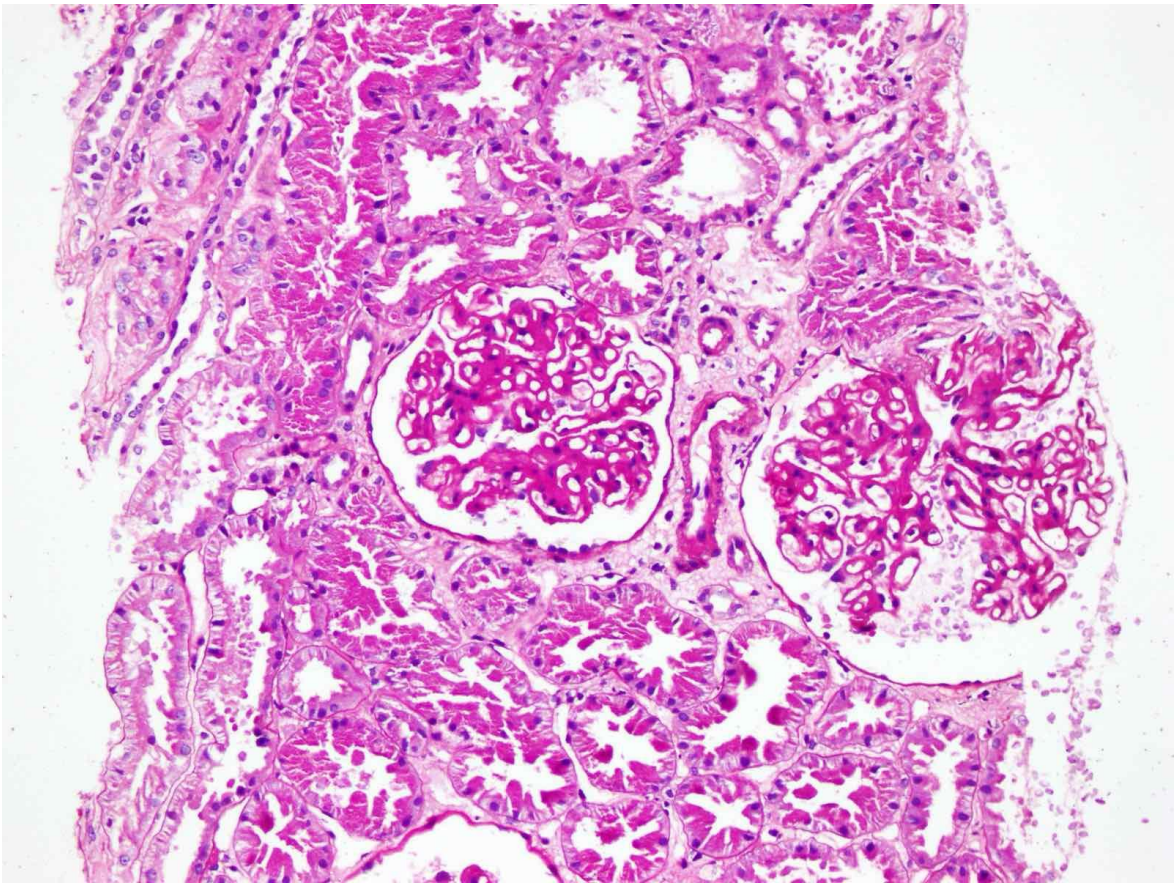


Photo (9) PAS stain highlights thickened glomerular basement membrane with mild mesangial expansion (PAS stain 20X)

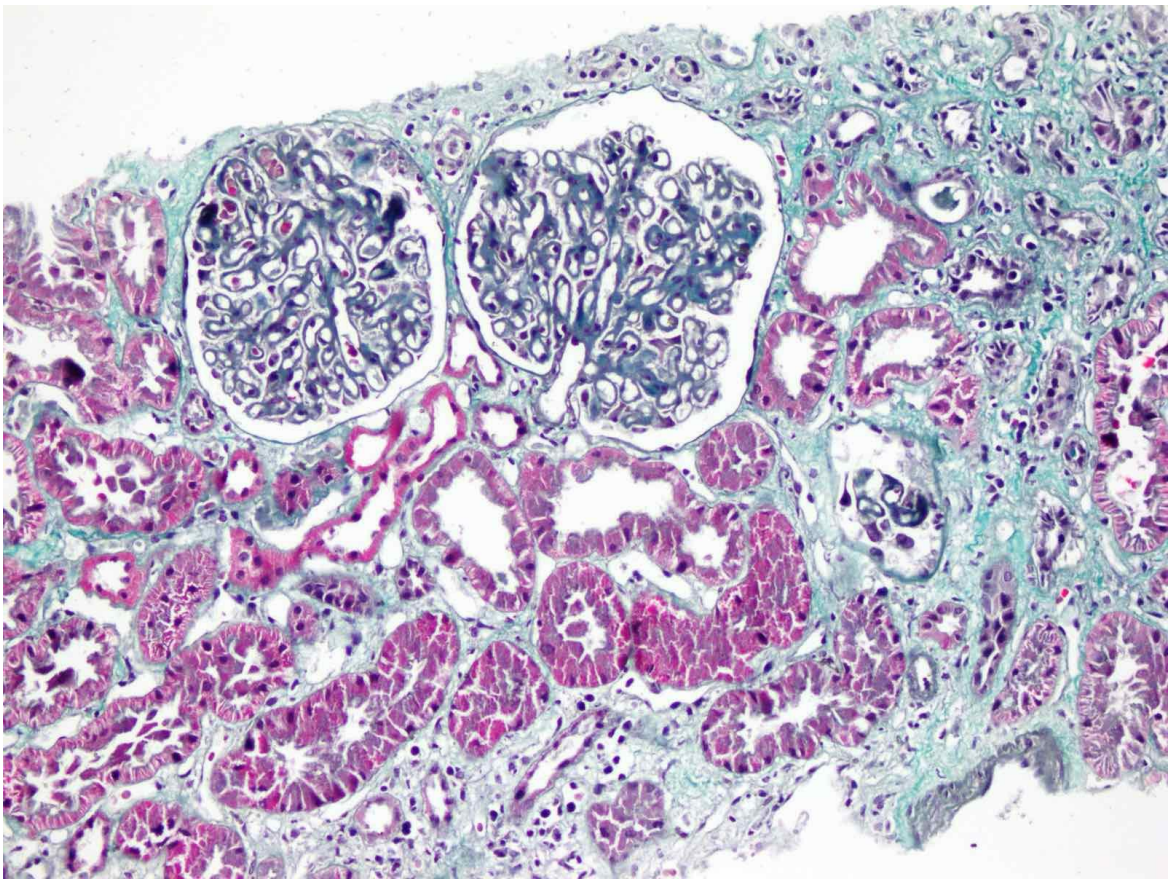


Photo (10) Mild interstitial fibrosis with scanty inflammatory cells between tubules (Trichrome stain 20X)

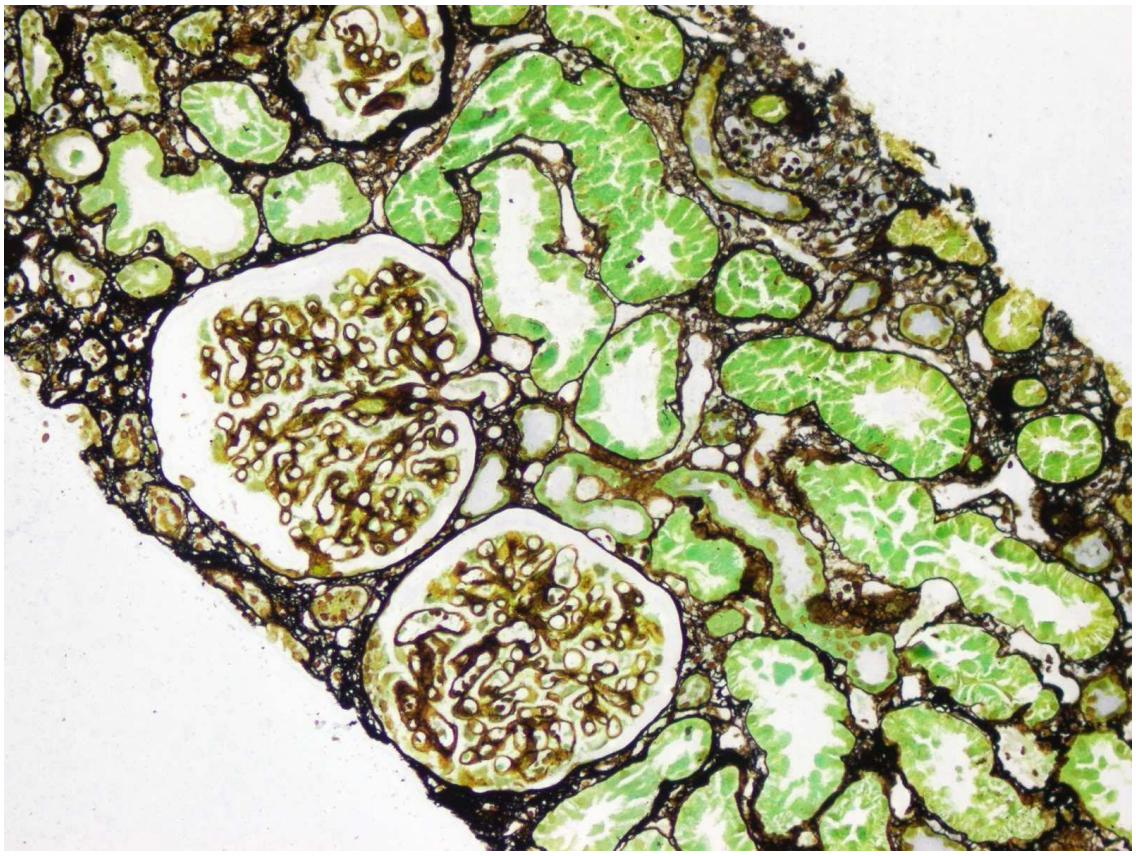


Photo (11) Numerous holes and spikes over glomerular basement membranes indicating membranous nephropathy (Silver stain 20X)

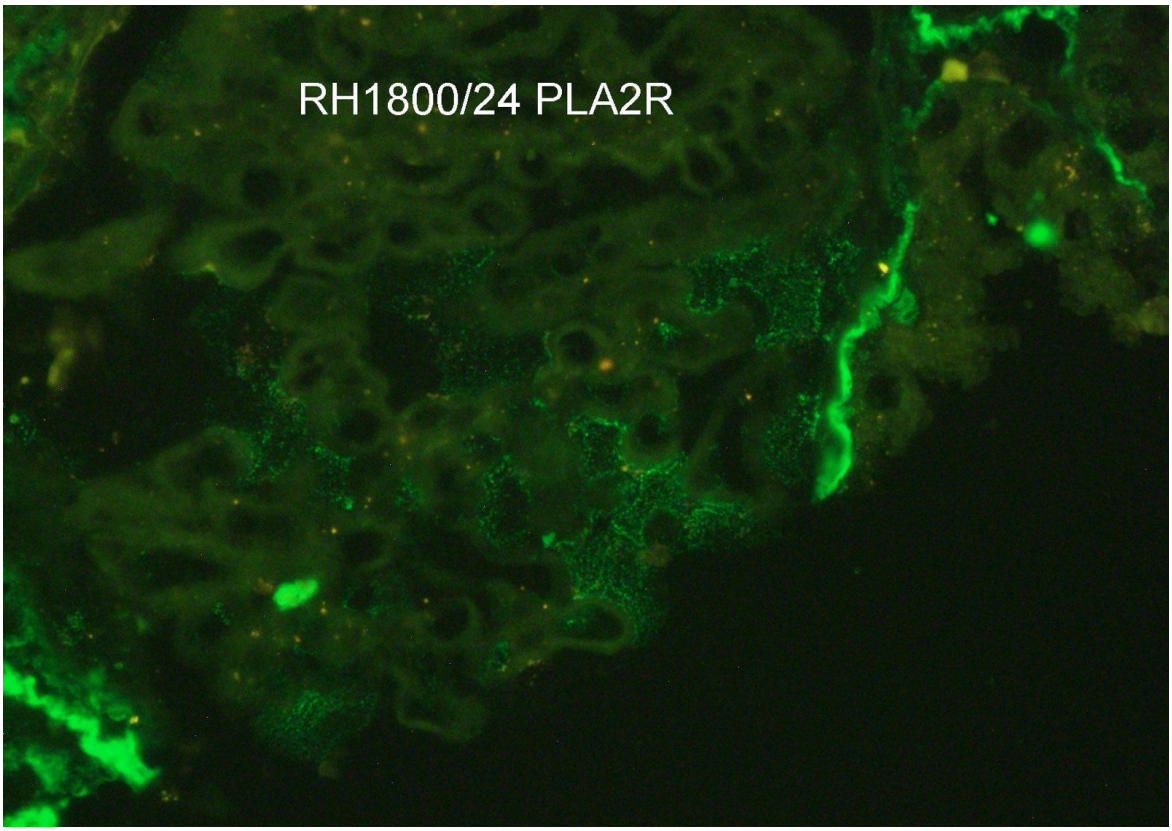


Photo (12) Immunofluorescence study done form FFPE tissue shows weakly positive fine granular PLA2R staining over glomerular basement membrane (Intensity 1+)

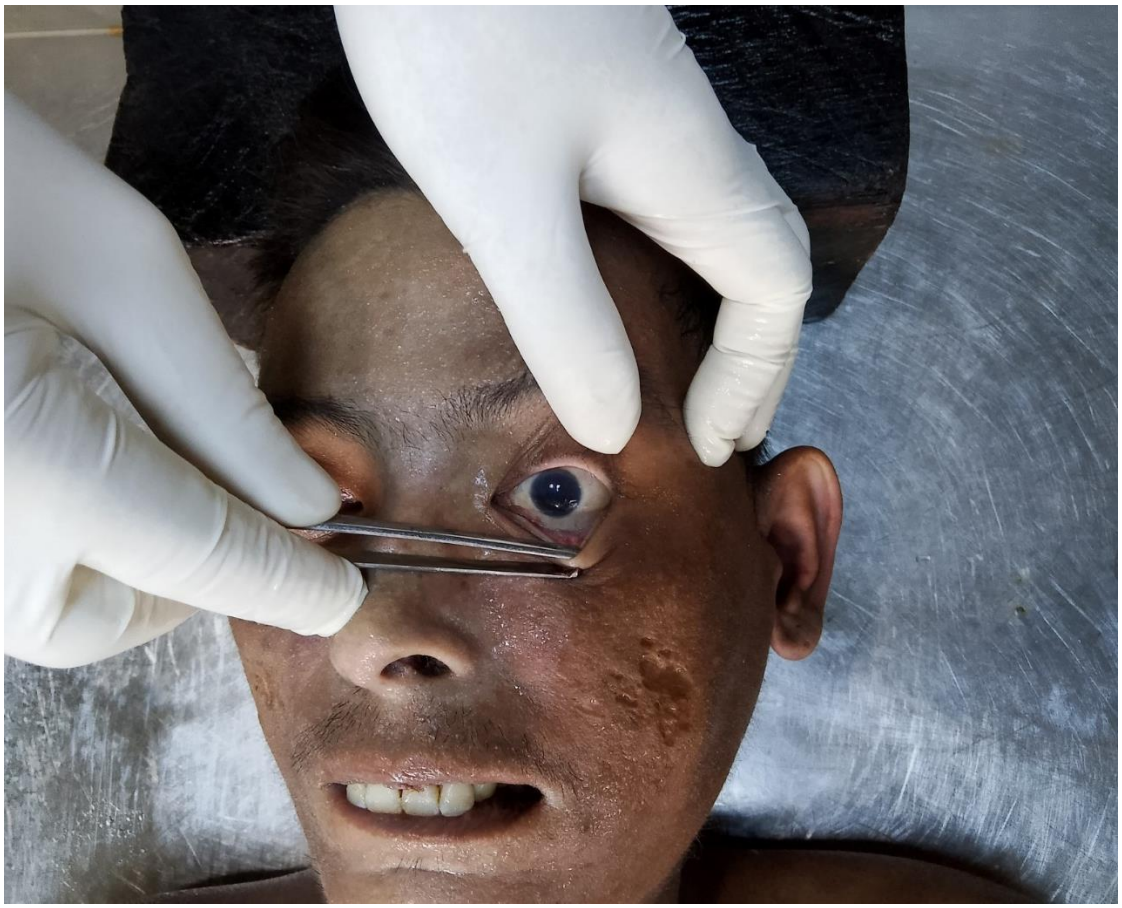


Photo (13) Autopsy of face showing anemia and multiple scars with dermal atrophy over both cheeks

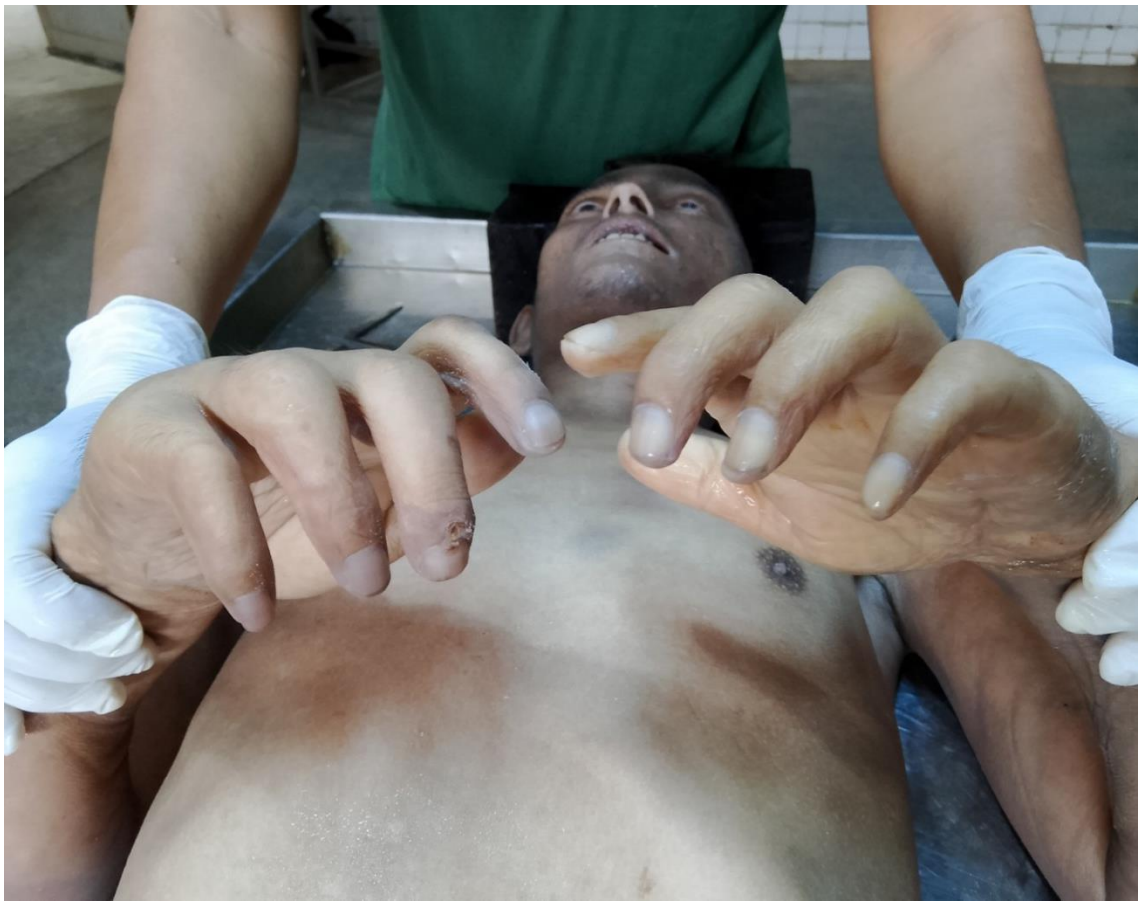


Photo (14) Autopsy of both hands showing terminal resorptions, deformity and vasculitis ulcer over right middle finger

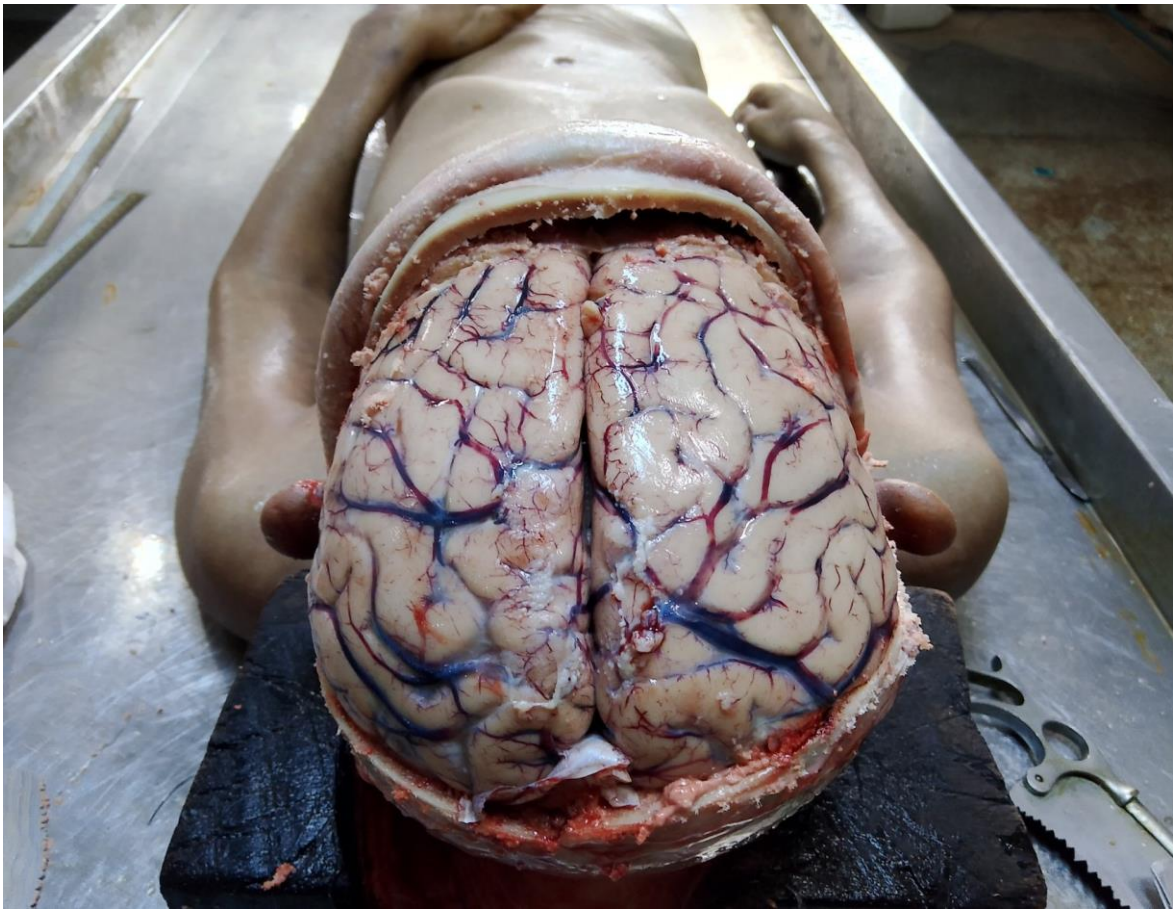


Photo (15) Autopsy of external surface of cortex of brain showing generalized marked cerebral oedema and congested veins

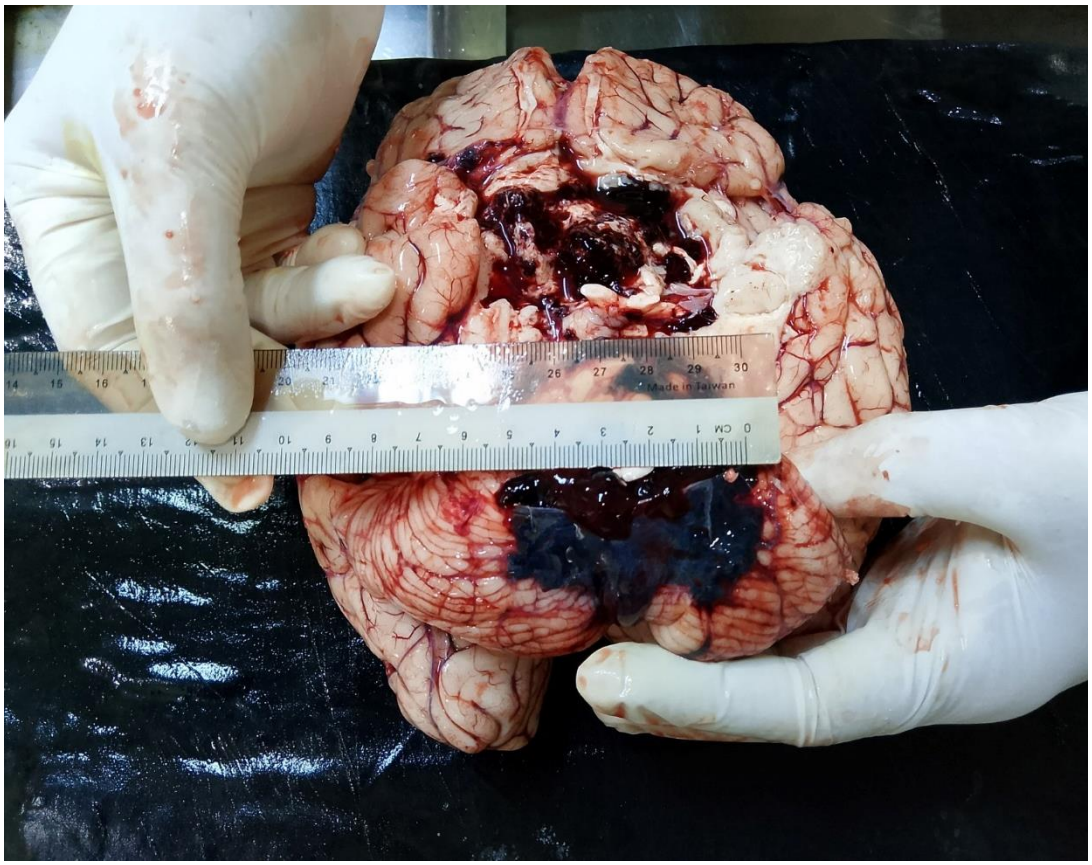


Photo (16) Autopsy of external surface of base of brain showing hematoma measuring 5 X 3 cm underneath the cerebellum, intracerebral hemorrhages at right parietal lobe and supratentorial and infratentorial hemorrhages

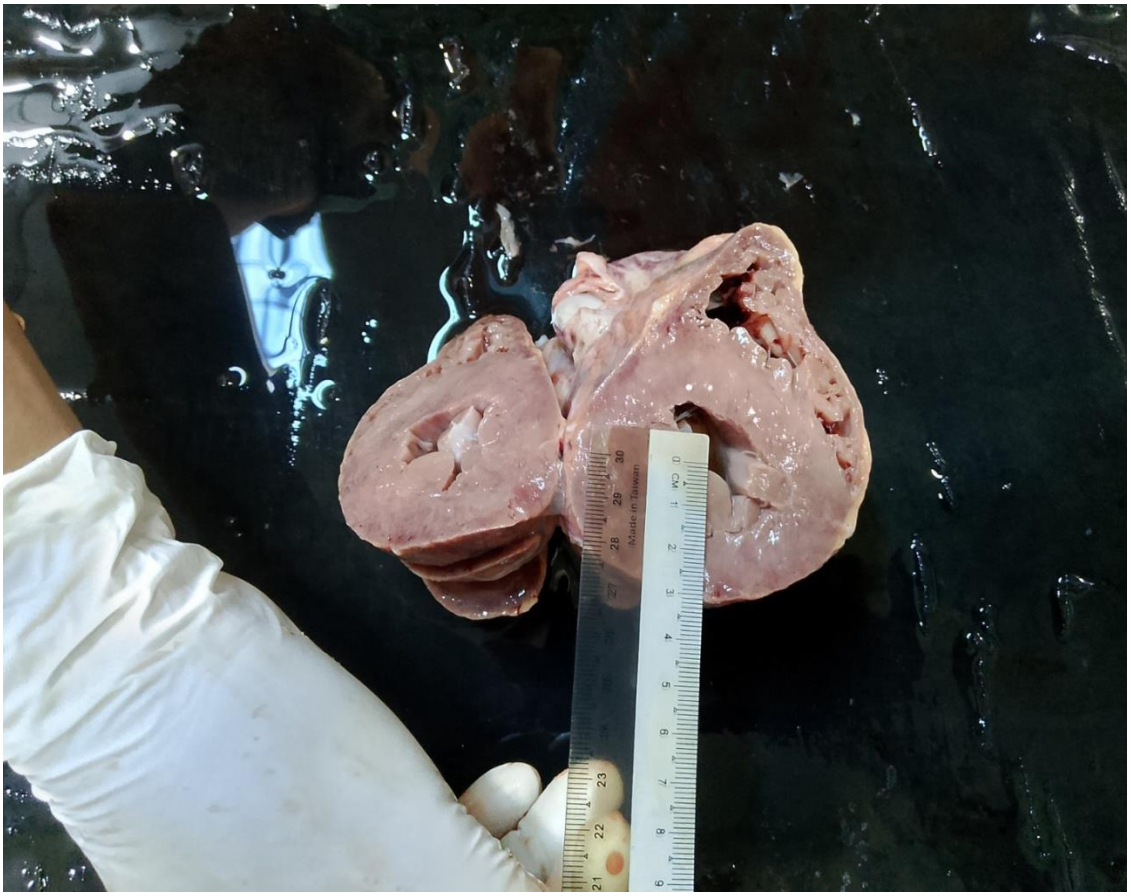


Photo (17) Autopsy of heart showing thickened left ventricular wall measuring 3.2 cm

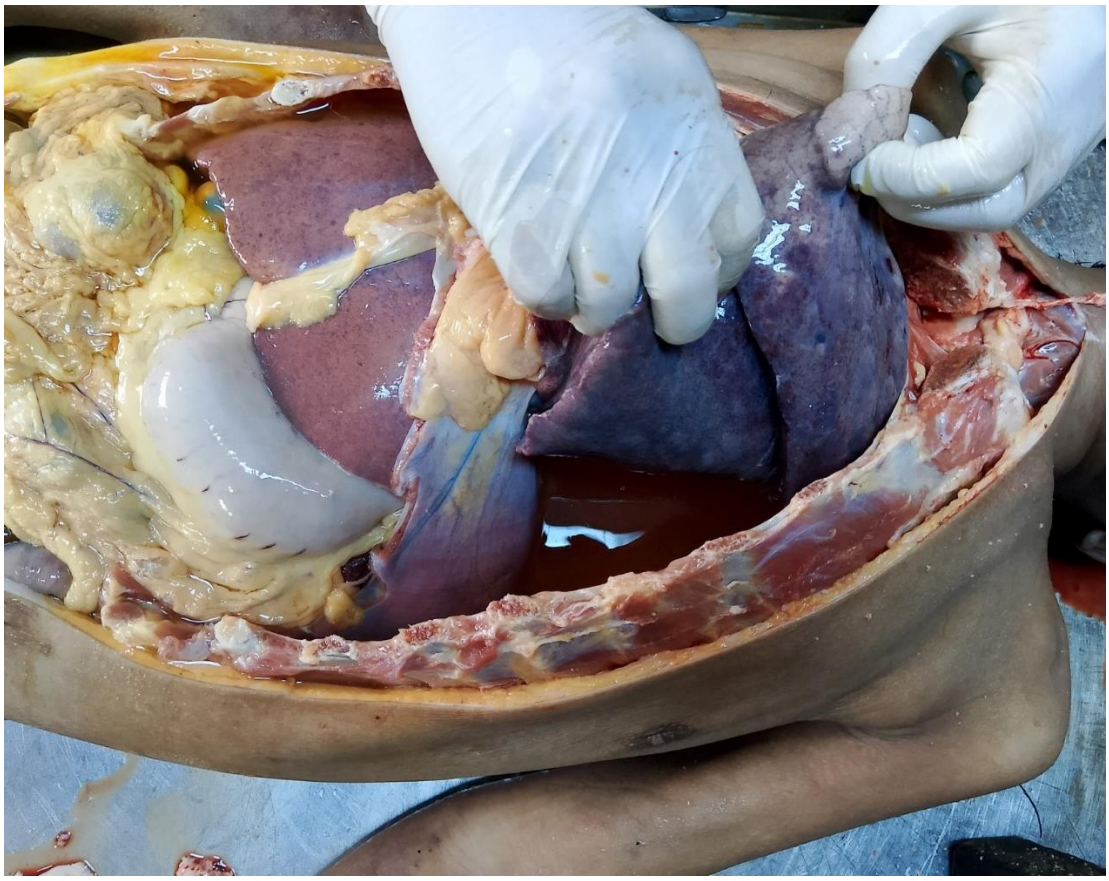


Photo (18) Autopsy of chest showing hemorrhagic pleural effusion on both side

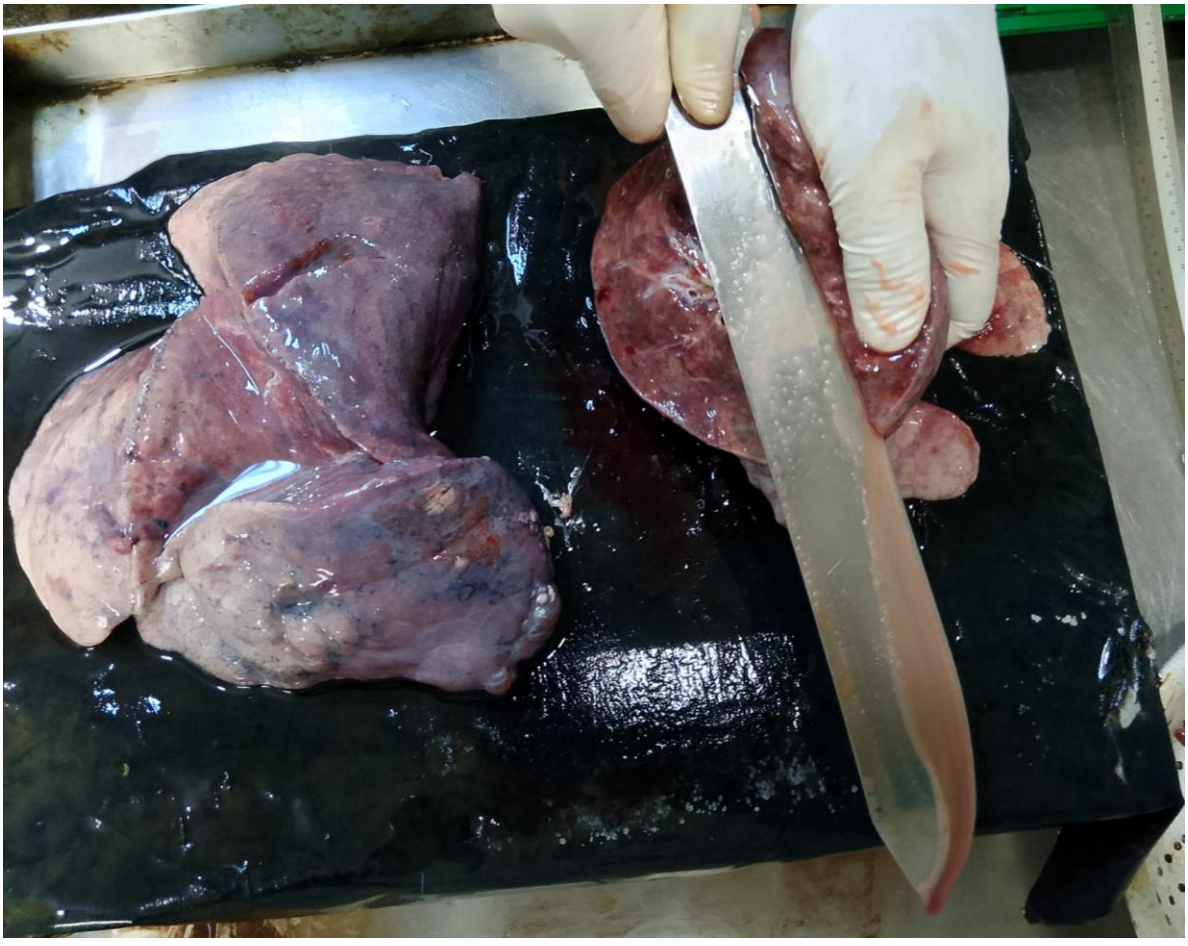


Photo (19) Autopsy of cut section of right lung with blood-stained serosanguinous fluids reflecting consolidation

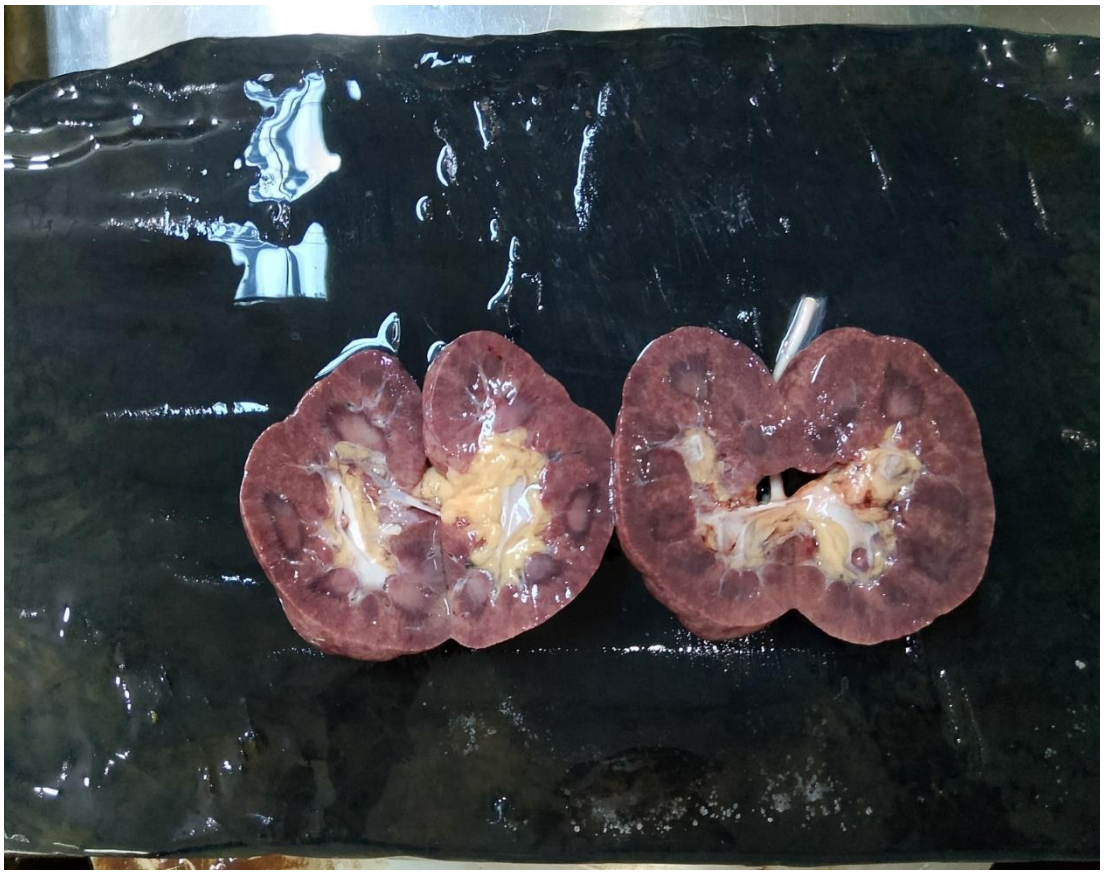


Photo (20) Autopsy of both kidneys, they were small with thin cortex and indistinct cortico-medullary junction suggestive of chronic glomerulonephritis

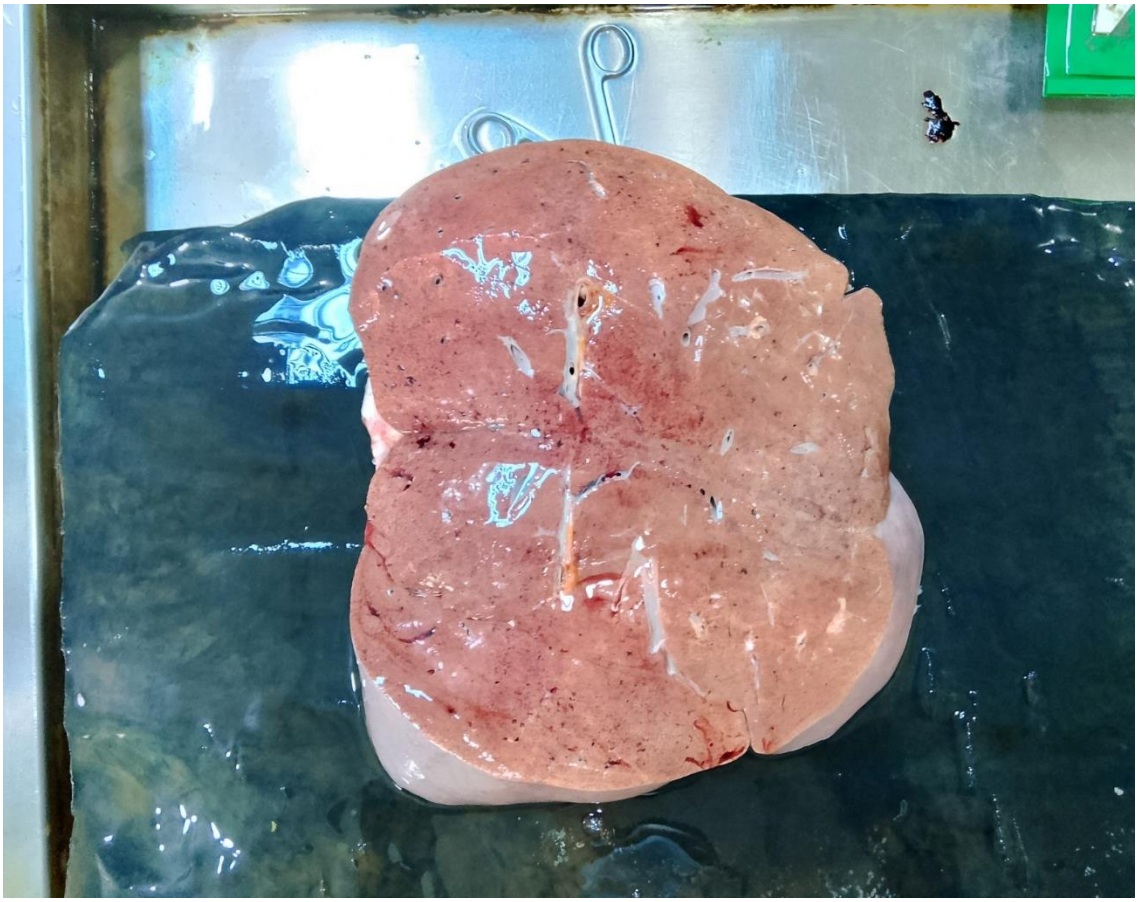


Photo (21) Autopsy of cut section of liver showing congestion

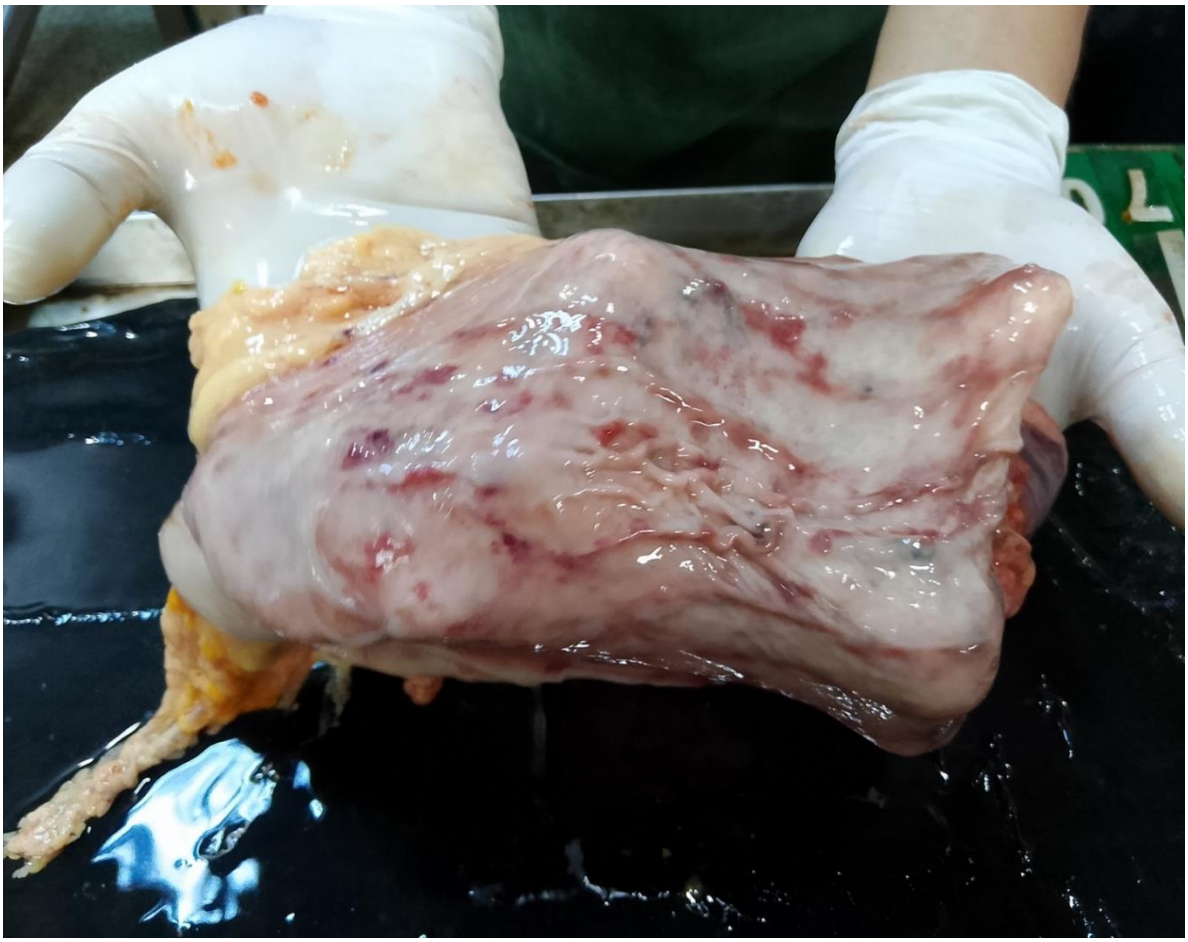


Photo (22) Autopsy of mucosa of stomach showing congestion and multiple shallow ulcers

Photo (23) Autopsy of cut section of spleen showing congestion and soft pulp suggestive of septic spleen