

Mesenteric Panniculitis and Rhabdomyolysis Complicated by Invasive Fungal Co-infection in a Case of Systemic Lupus Erythematosus: An Autopsy Report

Abstract

Invasive fungal infections are a significant cause of morbidity and mortality in patients with systemic lupus erythematosus. The case illustrates the autopsy findings in a patient with systemic lupus erythematosus complicated by multiple fungal infections. Rare, uncommon manifestations of SLE such as mesenteric panniculitis and rhabdomyolysis were also present. High index of suspicion with timely intervention with aggressive antifungal was life-saving.

Keywords: *Mesenteric panniculitis, rhabdomyolysis, systemic lupus erythematosus*

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with varied natural history and multisystemic involvement. It results from the complex interaction between genetic, hormonal factors, and environmental exposures with autoimmunity forming the cornerstone of its etiopathogenesis.^[1,2] With clinical presentations spanning a wide spectrum, the disease continues to be a great masquerader and is often a challenge for clinical diagnosis. The present case highlights two uncommon manifestations of SLE; mesenteric panniculitis and rhabdomyolysis. In addition, many of the systemic manifestations of SLE mimic those due to invasive fungal disease and thus making differential diagnosis difficult. The clinical course of the patient was complicated by co-infection with three fungi. The case also illustrates autopsy findings in various organs, some of which are classical and documented in annals of pathology literature. Although the last five decades have seen a marked improvement in the prognosis of SLE, an early diagnosis followed by adequate treatment measures is a game-changer.

Case report

A 25-year-old woman presented with fever of one-month duration, rash for

5 days, and abnormal body movements for past 2 days. The fever was intermittent in nature, moderate grade, relieved with medication and not associated with chills and rigors. The fever was accompanied by rash over face, upper trunk, limbs, palms, and fingertips for past 5 days. There was associated myalgia and arthralgia; however, there was no associated itching or pain. She had two episodes of generalized tonic/clonic body movements associated with urinary incontinence. Following the seizures, she became drowsy and was admitted to the hospital with altered sensorium. There was no history of decreased urine output, pedal edema, orthopnea, or chest pain. No history of vomiting, loose stools, hematemesis, malena, pain abdomen, hematuria, dysuria, pyuria or any bleeding manifestations. On examination, she was irritable and drowsy with E2M5V2, hypotension, tachypnea, tachycardia. There was no lymphadenopathy or edema. Malar rash and maculo-papular skin rash were noted with subconjunctival hemorrhage. Deep tendon reflexes were absent. Bilateral basal crepitations were noted. Cardiovascular system was normal. Liver was palpable 2 cm below the costal margin, while spleen was not palpable. Shifting dullness was noted. On investigations, she had anemia (8.1 g/dl) with leucocytosis ($11.1 \times 10^9/L$) and thrombocytopenia ($80 \times 10^9/L$); occasional schistocytes were noted

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in the peripheral blood smear. Her coagulogram indicated disseminated intravascular coagulation with positive D-dimer (3452 µg/L). She had hypoalbuminemia (1.1 g/dl) with deranged renal function; raised urea (126 mg/dl) and creatinine (2.8 mg/dl). Her liver function tests revealed raised alanine and aspartate aminotransferases (AST-4482 IU/l, ALT-278 IU/l, ALP-1031 IU/l, Total bilirubin 6.7 mg/dl.). She had evidence of rhabdomyolysis with raised creatinine kinase-NAC and MB levels (CK-NAC- 13585 mg/dl; CK-MB 112 mg/dl). She had laboratory evidence of hemophagocytosis with raised serum lactate dehydrogenase (4708 U/l), serum ferritin (16060 ng/ml), and triglycerides (587 mg/dl). Electrocardiogram revealed right axis deviation, low voltage complexes, and poor R wave progression and 2D ECHO performed revealed normal left ventricular systolic function, without any regurgitations or vegetations, clot, and emboli. Urine microscopic examination showed traces of albumin and sugar with occasional pus cells and RBCs. Urine myoglobin was positive. Chest X-ray revealed bilateral diffuse infiltrates. Viral markers (Hepatitis B, A, C, and E) were negative. Autoimmune work-up revealed positive antinuclear autoantibody (ANA-2 to 3+, centromeric pattern with positive dsDNA (411.2 IU/ml). Antiphospholipid lupus antibodies (both IgG and IgM) were negative and C3 and C4 levels were normal. Blood and urine cultures were sterile. Serology for malaria,

dengue, scrub typhus, typhoid, and *Leptospira* was negative. Preterminal blood culture showed the growth of *Acinetobacter baumannii*, *S. aureus*, and *Candida albicans*.

A possibility of connective tissue disorder with multiorgan involvement, likely SLE, was kept and she was started on phenytoin, ceftriaxone, and doxycycline. Intravenous fluids and vasopressors were given for shock. She developed upper GI bleed for which she was managed with transfusions with blood products. Steroids (pulse methyl prednisolone) were started subsequently in view of downhill course with recurrence of seizures, massive hemorrhage, and persisting fever. Despite all the measures, she succumbed to her illness.

Autopsy findings

A complete autopsy performed after an informed consent revealed the presence of ascites (1500 ml) and pleural effusion (500 ml). Pathological features of SLE were noticed in various organs, most remarkably in *kidneys* which weighed 360 g. On gross examination, apart from small pin-point hemorrhagic spots noted in the cortex, the rest of kidneys were normal. Microscopically, kidney revealed evidence of class II lupus nephritis, with mesangial and subendothelial deposits on electron microscopy [Figure 1a-c]. Direct immunofluorescence performed on the kidney tissue showed a full-house

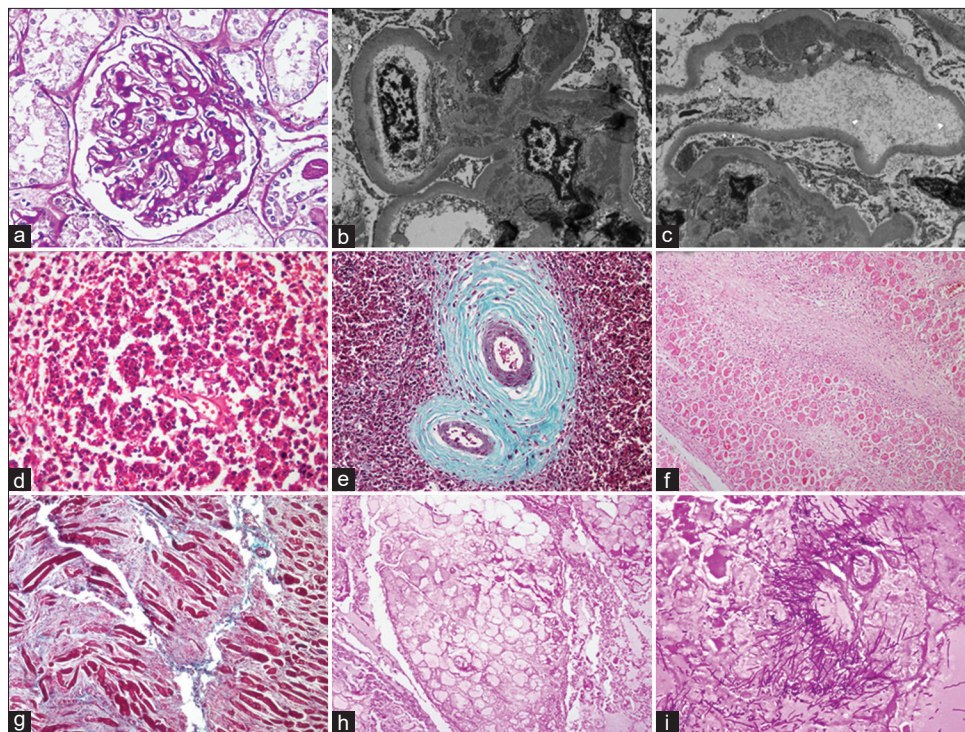


Figure 1: a-c: Lupus nephritis, class II. Mild mesangial expansion (a: Periodic acid-Schiff's, [PAS] ×100), with mesangial and subendothelial deposits on electron microscopy (b, c: Uranyl acetate with lead citrate × 1500); d: Germinal center of the lymph node showing nuclear debris (hematoxylin and eosin, H and E ×400); e: Masson's trichrome stain highlights prominent onion skinning around the splenic arterioles (Masson's trichrome, MT ×200); f: Section of psoas muscle demonstrates necrosis and destruction of the muscle fibers (H and E ×100); g: Masson's trichrome stain highlights loss of muscle fibers secondary to destruction (MT ×200); h: Extensive areas depicting mesenteric panniculitis with necrosis of mesenteric fat (H and E ×200); i: Colonies of pseudohyphae of *Candida* invading the mesenteric fat in a background of fat necrosis (PAS ×200)

pattern with 3+ positivity for antisera specific for IgG, IgA, IgM, C3, kappa, lambda, and C1q along mesangium, subendothelium, and glomerular capillary loops. There was no evidence of any extraglomerular deposits. A few pigment casts were also identified which were accompanied by moderate degree of acute tubular injury. The vascular compartment was within normal limits; however, the interstitium showed multiple candidal micro abscesses. Peri-pancreatic *lymph nodes* were enlarged (1–1.5 cm) with firm consistency and grayish-white cut-surface, which was variably hemorrhagic and necrotic. The lymph node microscopically revealed necrotizing lupus lymphadenitis with extensive necrosis and characteristic “hematoxyphilic” debris [Figure 1d]. Hemophagocytosis was also noted within the follicles and also in the bone marrow. *Spleen* weighed 100 g and on microscopy features typical “onion-skinning” around arterioles [Figure 1e] and nuclear debris collection both within white and red pulp. *Liver* weighed 1200 g with normal cut surface. On microscopy, liver revealed features of ischemic hepatitis in form of centrilobular congestion, necrosis of hepatocytes with condensation of reticulin fibers. *Pancreas* was essentially normal but for presence of hemorrhagic, fat necrosis noted around peri-pancreatic region. Psoas muscle sampled revealed features of myonecrosis and inflammatory myopathy [Figure 1f and g]. *Esophagus* was within normal

limits; however, the mucosa over stomach showed multiple tiny (8–10 mm) ulcers which microscopically revealed the presence of yeast and pseudo-hyphal form of candida with evidence of angio-invasion. Mucosal aspect of *small intestine* was normal; however, extensive fat necrosis was noted along the serosal aspect [Figure 1h and i]. Likewise, *large intestine* showed extensive fat necrosis on serosal side, which revealed extensive areas of fat necrosis with invasive candida infection. However, mesenteric vessels were within normal limits. No thrombosis or vasculitis was noted. Both *lungs* weighed 1100 g. They were heavy and with diffuse areas of marked consolidation along with infarcts. Mucosa over trachea was ulcerated with the presence of candida pseudo-hyphae. Microscopically, lung demonstrated extensive alveolar hemorrhage, lobar bronchopneumonia, features of diffuse alveolar damage and pulmonary edema. Occasional fungal abscess colonized by *Aspergillus* and *Candida* was also seen [Figure 2d-f]. The pulmonary vessels were within normal limits. *Candida* had disseminated to involve the kidney with formation of small micro abscesses in the cortex [Figure 2g], myocardium [Figure 2h], stomach, and small and large intestine [Figure 2i]. The *heart* weighed 180 g. Grossly, all chambers and valves were within normal limits. Microscopy of heart also revealed fungal (*Candida*) myocardial abscesses. The *brain* weighed 1380 gm. Gross

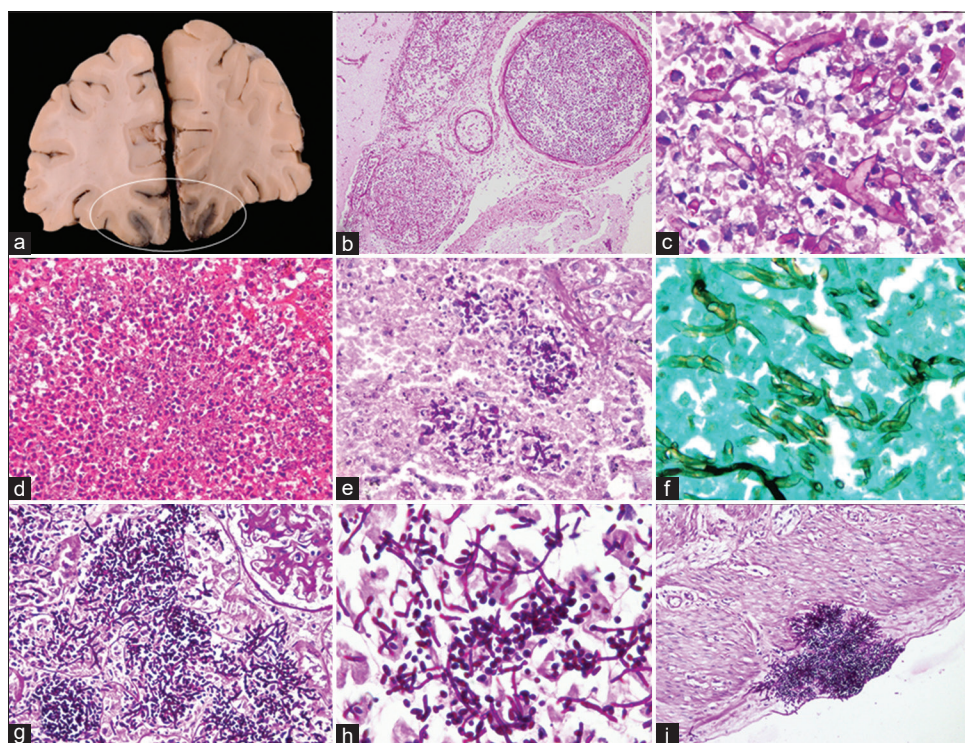


Figure 2: (a) Coronal slice of the brain depicting hemorrhagic necrosis of the cortex near the orbital surface of frontal lobe (white circle); (b) Prominent thrombosed vessels in the subarachnoid space filled with fungal hyphae (PAS $\times 200$); (c) Broad, aseptate fungal hyphae with morphology conforming to *Mucor* within the thrombosed blood vessels (PAS $\times 1000$); (d) Microphotograph of the lung depicting features of bronchopneumonia with microabscess formation (H and E $\times 400$); (e) PAS stain highlights the yeast and pseudohyphal form of *Candida* within these microabscesses (PAS $\times 400$); (f) Few septate, slender, branching hyphae of *Aspergillus* were also detected within the lung parenchyma (Grocott's methenamine silver $\times 1000$); (g) Candidal abscess seen within the renal parenchyma (PAS $\times 400$); (h) *Candida* pseudohyphae destroying the cardiac myocytes (PAS $\times 1000$); (i) *Candida* colonies growing along the serosa of the large intestine

as well as microscopic examination revealed the presence of cerebral mucormycosis (meningitis and encephalitis) with early cortical infarcts and thrombosed meningeal vessels filled with broad, aseptate *Mucor* hyphae [Figure 2a-c]. No hyphal forms of *Aspergillus* or *Candida* were identified in brain. The abdominal skin biopsy revealed leucocytoclastic vasculitis with full-house pattern of staining on direct immunofluorescence.

Thereby, the final diagnosis of Systemic lupus erythematosus with lupus nephritis (Class II) with necrotizing lupus lymphadenitis, hemophagocytosis, and disseminated intravascular coagulation, mesenteric panniculitis causing extensive fat necrosis was given. In addition, she had co-infection with *Candida* (with micro abscesses in lungs with dissemination to stomach, kidneys, heart, peritoneum), lobar bronchopneumonia, diffuse alveolar hemorrhage with fungal (*Aspergillus*) abscess and cerebral mucormycosis with early cortical infarcts along with rhabdomyolysis causing pigment cast nephropathy and acute tubular necrosis.

Discussion

SLE is well known to be a great multisystemic masquerader as illustrated yet again by this case. The two interesting and uncommon findings which this case highlights are mesenteric panniculitis and rhabdomyolysis. While lupus panniculitis *per se* is a well-known cutaneous manifestation of SLE^[3] and has often been reported over the years, mesenteric panniculitis has seldom been reported.^[4-7] This as an initial presentation is a rare event with only two documented cases in the literature.^[4,5] It usually arises on a backdrop of any kind of trauma, abdominal malignancy, autoimmune disorders, ischemia, or previous abdominal surgery^[8] and is characterized by inflammatory cell destruction of adipose tissue of the mesentery. Morphologically, it features lymphocytic infiltrate involving fat lobules and hyaline necrosis of the fat lobule accompanied by nuclear debris within the infiltrate.^[9] Panniculitis extensively affecting the mesenteric fat in the index case was complicated by invasive candidiasis. Respiratory tract is the commonest portal of entry for fungal infection which later disseminated extensively to involve other organs. Candidal abscesses classically are micro abscesses with neutrophil-rich center as seen in this case. *Candida* infection and its widespread dissemination to various organs appears to be relatively long-standing as compared to *Aspergillus* and *Mucor* by virtue of its lesser pathogenicity. We postulate that mesenteric panniculitis increased the gut permeability, which subsequently led to candidal translocation and candidemia. Candidal colonization of the gut is the likely pathway for the development of disseminated candidal abscesses in this patient. However, the presence of tracheal ulcers with *Candida* hyphae favors lung as an additional portal of entry for *Candida*. We speculate that infection

by lung abscess colonized by *Aspergillus* and cerebral Mucormycosis with its angio-invasion was a recent, preterminal event, as both these fungal infections have high pathogenicity with very rapid dissemination. While no focus of *Mucor* was identified in the lung despite extensive sampling, the respiratory route remains the commonest portal of entry and further sampling could have confirmed its presence in lungs. Active lupus disease in itself is a risk factor for invasive fungal infections. In addition, the steroidal treatment which she received further compromised her immune status. Furthermore, normal flora of *Candida* in patient's body took advantage of the immunosuppression and rendered her vulnerable to infections with *Aspergillus* as well as *Mucor*. Invasive fungal disease is common in SLE and reported in 86% of the lupus patients during the active disease stage.^[10] It is associated with high mortality. Co-infection is not uncommon and in a recent study by Lao *et al.* it occurred in 26.7% of the patients.^[11] Their findings indicate that higher accumulated dose of glucocorticoids and lymphopenia (both T and B cells) are risk factors for the development of invasive fungal disease. Immune defects in untreated SLE which predispose to infections include impairments in phagocytic functions (superoxide deficits and defective phagocytosis), cytokine expression (decreased IL 2, increased IL10 and TNF- α), complement activation and cellular (impaired T cell cytotoxic capability, lymphopenia, and NK cell dysregulation) as well as humoral immunity (hypogammaglobulinemia and B cell maturation flaws).^[12] Moreover, susceptibility to infections also increases due to end-organ tissue damage in SLE.

Other well documented pathological features of SLE such as lupus nephritis, necrotizing lymphadenitis with hematoxyphilic debris, leucocytoclastic vasculitis, and onion-skinning of splenic arterioles were also noted. Lupus nephritis was categorized as Class II with mild mesangial expansion and presence of subendothelial and mesangial electron-dense deposits on electron microscopy.

Rhabdomyolysis, as noted in this case is another rare potentially lethal manifestation reported in patients with SLE.^[13-15] Various factors implicated in the causation of non-exertional rhabdomyolysis include drugs, inflammatory disorders, and infection.^[13,15] Rhabdomyolysis is defined by markedly high levels of the enzyme—creatinine kinase (CK)—and myoglobinuria eventually led to renal dysfunction due to pigment cast nephropathy and acute tubular injury. Underlying infections (both bacterial and fungal) could also be the triggering event in its causation.

Clinical symptoms of altered sensorium and seizure which the patient developed preterminally due to cerebral mucormycosis mimicked the neuropsychiatric manifestations of SLE. However, these are the least understood and most prevalent manifestations. Pathogenesis of neuropsychiatric SLE is multifactorial and involves various cytokines and autoantibodies resulting

in vasculopathic, cytotoxic, and autoantibody mediated neuronal injury.^[16] The subarachnoid and intraparenchymal vessels demonstrated fibrin-rich thrombi and many were clogged by *Mucor* hyphae. No significant demyelination was detected in the central white matter.

In conclusion, the index case highlights infection with three fungus as the compromised immunity converted the body into a culture media for fungal pathogens. Such cases need to be identified with high index of suspicion and managed with aggressive supportive care and antifungal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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