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PAPER

PATHOLOGY/BIOLOGY

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Lethal Manifestations of Systemic Lupus Erythematosus in a Forensic Context

ABSTRACT: Systemic lupus erythematosus is an autoimmune connective tissue disorder that affects multiple organs. While the clinical manifestations may vary in intensity over time and be associated with chronic disease, occasional cases occur where sudden and unexpected death has occurred. Cardiovascular disease is common, with accelerated atherosclerosis, intravascular thrombosis associated with antiphospholipid syndrome, and hypertensive cardiomegaly. Vasculitis with superimposed thrombosis may result in critical reduction in blood to vital organs, such as the heart and brain with infarction. Mesenteric ischemia may be caused by vasculitis, thrombosis, and accelerated atherosclerosis and may result in lethal intestinal infarction. Other diverse causes of sudden death include myocarditis, epilepsy, pulmonary hypertension, pulmonary thromboembolism, and sepsis. The autopsy evaluation of such cases requires careful examination of all organs with extensive histological sampling to include blood vessels, and microbiological sampling for bacteria, viruses, and fungi.

KEYWORDS: forensic science, systemic lupus erythematosus, sudden death, myocarditis, antiphospholipid syndrome, thromboembolism

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disorder characterized by multiorgan damage mediated by immune complexes and autoantibodies (1). Although it most commonly manifests between the ages 15 and 40 years, it may affect people of any age resulting in subclassifications of neonatal, pediatric, and late-onset (>50 years of age) SLE (2). SLE involves multiple organ systems resulting in a plethora of clinical manifestations, the clinical course and severity of which vary substantially between individuals. Generally, it is characterized by disease "flare" and remission states. While patients with SLE tend to have protracted clinical courses, certain manifestations may result in quite rapid and unexpected deaths, and thus bring the victim to medico-legal autopsy; an understanding of SLE is thus required in forensic practice. However, despite extensive clinical literature, there has been little written in the forensic literature on aspects of the condition that results in such an outcome. This study provides an analysis of manifestations and lethal mechanisms of SLE that may lead to sudden death, including a detailed review of the current understanding of its pathogenesis.

Prevalence

The prevalence of SLE in Europe and the U.S. ranges from 14.6 to 68 per 100,000 of the population, with a higher incidence in women, especially those of childbearing age (3). It is estimated that women are nine to 12 times more likely to develop the disease than men. The annual incidence of SLE in developed countries has increased 10-fold over the last 50 years, believed to be because of both improved detection of the disease and an actual increase in disease incidence (4). Ethnic differences are also noted, with non-Caucasian populations having a greatest risk of developing SLE; the highest prevalence being found in African-American and Asian populations. As this increase in prevalence is not reflected in African populations in Africa itself, social and environmental factors may influence the induction of the disease (2).

Etiology

Although the exact etiology and pathogenesis of SLE remain uncertain, a number of theories have been postulated. Suggested risk factors include a combination of genetic influences, viral infections, hormonal imbalances, and environmental stimulants (2). These are thought to result in the production of autoantibodies and immune complexes, subsequently triggering a cascade of inflammatory events leading to tissue damage and fibrosis (5).

The abnormal immunological reactions leading to the development of SLE most likely involve numerous defective mechanisms including increased activation of T and B lymphocytes and decreased production of regulatory T cells (CD4, CD8). The activation of dendritic cells by immune complexes and autoantigens, followed by reduced clearance of apoptotic cells and immune complexes is thought to lead to sustained production of autoantibodies. This compounded by increased secretion of proinflammatory mediators results in a prolonged inflammatory response and subsequent disease development (6–11).

A genetic contribution to SLE has been shown, with 12% of patients having a first-degree relative affected by the condition. Human leukocyte antigens (HLA) class I, II (HLA-DR2, HLA-DR3), and III that are responsible for encoding antigen-presenting cells, tumor necrosis factor (TNF), and complement components, have an association with production of autoantibodies. Although HLA associations are well established in SLE, it is possible that an array of genetic polymorphisms increase individual susceptibility to the

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condition by enhancing immune response to specific stimuli (1). Viruses, such as cytomegalovirus (CMV), Epstein-Barr (EBV), and parvovirus, could then act as triggers for SLE in certain individuals (12).

Mechanisms are poorly understood, but EBV provides possible clues, as EBV nuclear antigen-1 shares similar protein conformations to host self-antigens, leading to the production of Ro and Sm autoantibodies by the process of molecular mimicry (8). The virus also remains latent in the B cells of its host throughout life after active infection thus raising the possibility of further autoantibody production (13). Not all people who have EBV infections develop SLE, which indicates that the virus is not solely responsible for causing the disease. However, a study by James et al. (13) has confirmed concordance between SLE and previous infection.

Hormonal factors have recently been implicated in the pathogenesis of the disease and may explain the higher incidence of SLE in fertile female populations. For example, elevated levels of estrogen or prolactin are thought to increase the activity of autoreactive B cells by interfering with B-cell tolerance (14).

Diagnosis and Outcome

The diagnosis of SLE during life depends on the finding of certain manifestations and criteria that are summarized in Table 1 (15,16). Laboratory diagnosis requires a typical constellation of immunological derangements with elevated autoantibodies including ANA, anti-SM, anti-dsDNA, and anti-SSA (Ro) or anti-SSB (La) antibodies, often associated with reduced levels of C2 and C4. More general inflammatory markers may also be useful with elevated erythrocyte sedimentation and C-reactive protein levels. It is also possible that identifying specific genetic polymorphisms may assist in identifying disease susceptibility and severity (17).

TABLE 1—*Diagnostic criteria for systemic lupus erythematosus (SLE).*

Criteria	Description
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging
Photosensitivity	Rash occurring after exposure to sunlight
Oral ulcers	Oral and nasopharyngeal ulcers confirmed on clinical examination
Arthritis	Nonerosive arthritis involving two or more peripheral joints with tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis on ECG or by rub or effusion
Renal disorder	Persistent proteinuria >0.5 g/day or cellular casts
Neurological disorder	Seizures or psychosis in the absence of offending drugs or metabolic derangement
Hematological disorder	Hemolytic anemia with reticulocytosis or leukopenia (<4000/μL) on two or more occasions, or lymphopenia (<1500/μL) on two or more occasions, or thrombocytopenia (<100,000/μL) in the absence of offending drugs
Immunological disorder	Anti-dsDNA, anti-Sm, and/or antiphospholipid
Antinuclear antibodies	Abnormal antinuclear antibody titer by immunofluorescence or equivalent assay at any point in time with the absence of drugs associated with drug-induced lupus

Any combination of ≥4 of the mentioned 11 criteria is characteristic of SLE. Adapted from American College of Rheumatology criteria for classification of systemic lupus erythematosus (15,16).

Remission is induced and maintained in affected individuals by drug treatments that target various immune processes. While permanent remission may be achieved, this is not always possible (18,19). In recent years, the introduction of immunosuppressive agents has contributed to an improved long-term prognosis of SLE with an estimated 5-year survival, now >95%, compared to that of 50 years ago, when it was <50%. However, the mortality is still 3–5 times higher than that of the general population, with the leading causes of death being cardiovascular disease, cerebrovascular disease, and infection (3,20).

Individuals with SLE may present to autopsy for a number of reasons. One involves the multifactorial nature of the underlying disease processes, with attending doctors being unable to determine the precise cause of death because of the complexity and subtlety of manifestations (21). An autopsy may also be required if death is unexpected.

Sudden Death

Sudden death may result from a variety of processes. For example, it may be directly because of the effects of the disease process or some aspect of treatment. Alternatively, it may be attributed to an entirely coincidental and unrelated disease process or accident, or it may be attributed to self-inflicted injury associated with depression induced by chronic illness. Possible features of SLE that may be found at autopsy associated with sudden and/or unexpected death are summarized in Table 2.

Cardiovascular Disease

Cardiac complications in SLE are found in every anatomical region of the heart and manifest as pericarditis, endocarditis, myocarditis, coronary arteritis, coronary vascular disease, cardiac arrhythmias, conduction disturbances, and congestive heart failure

TABLE 2—*Manifestations and characteristics of systemic lupus erythematosus that may be responsible for sudden and/or unexpected death.*

Cardiac
Myocarditis
Myocardial ischemia/infarction
Endocarditis
Vascular
Pulmonary embolism
Pulmonary hypertension
Vasculitis
Dissecting/ruptured aortic aneurysm
Pulmonary
Hemorrhage
Pneumothorax
Cerebral
Ischemia/infarct
Hemorrhage
Epilepsy
Gastrointestinal
Intestinal vasculitis
Acute pancreatitis
Mesenteric ischemia/infarction
Infection
Viral
Bacterial
Fungal
Hematological
Antiphospholipid syndrome
Genitourinary
Renal hypertension
Miscellaneous
Combination of factors

(22). The underlying pathophysiology by which SLE predisposes patients to an increased susceptibility to such conditions is varied and complex. Vasculitis, accelerated atherosclerosis, renal hypertension, and the presence of antiphospholipid antibodies are all involved (23). These, combined with general risk factors for heart disease and other noncardiac pathology related to SLE, greatly increase the prevalence of cardiac morbidity and mortality. Sudden death because of cardiac manifestations may therefore occur as a result of acute myocarditis, myocardial ischemia/infarction, and endocarditis.

Myocarditis

Myocarditis is now a rare cause of sudden death because of improved echocardiography and immunosuppressive agents (24). While asymptomatic myocarditis may have been suspected clinically if global hypokinesia was observed on an echocardiogram (25), the diagnosis may not be made until autopsy. It has been reported that 40% of cases of SLE may have the evidence of myocarditis at autopsy (26). Conversely, Wijetunga and Rockson (24) have shown that the prevalence of myocarditis has dropped to about 7%, compared to 57% 40 years ago.

It is important to adequately sample the heart at autopsy as histological findings may be focal, with variable numbers of lymphocytes, mononuclear and plasma cells, and patchy fibrinoid degeneration of collagen fibers, interstitial edema, myocyte necrosis, and diffuse immune complex disposition in perivascular areas (22,24). Although sudden cardiac death from acute myocarditis-induced arrhythmia in patients with SLE may be attributed to myocyte necrosis, as in other cases of myocarditis, it may also be attributed to immune complex disposition and inflammation of the myocardium without direct myofibril damage (24). Chronic progressive myocarditis leading to unexpected death was reported by Takahashi et al. (27) in a patient with a history of myocardial fibrosis.

Myocardial Ischemia/Infarction

Myocardial infarction is a common cause of unexpected death in the general population and is also an important cause in patients with SLE. However, myocardial infarction may occur at any age in SLE; for example, Ishikawa et al. (28) reported a 5-year-old girl who died suddenly of an acute myocardial infarct resulting from coronary atherosclerosis with thrombus formation in the left coronary artery. Both long-term prednisolone therapy and vasculitis were considered contributing factors.

A review by Karrar et al. (23) reported that women with SLE had an incidence of myocardial infarction 50 times higher than that of age-matched controls in the general population, and at a much younger age. This increased incidence is contributed to by accelerated atherosclerosis, antiphospholipid syndrome, and vasculitis. Death results from myocardial ischemia and rarely spontaneous cardiac rupture. For example, Takayanagi et al. (29) reported a 33-year-old woman who presented with severe left anterior chest pain and was diagnosed with a myocardial infarct. She died unexpectedly 22 days later, and at autopsy she was found to have extensive atherosclerosis and coronary arteritis resulting in a recent myocardial infarct of the left ventricular wall with rupture and a hemopericardium.

While the etiology of atherosclerosis is not completely clear, it does involve an inflammatory process characterized by activated immune cells within the arterial intima (30). It is believed that chronic systemic inflammation in SLE damages the arterial wall and exacerbates this process (31). Ischemic cardiovascular disease related to thrombosis and unstable plaque rupture may be exacerbated by cytokines, such as TNFα and IFN-γ, that are abundant in such plaques (30). While patients who have had the most steroid treatment have a greater chance of developing atherosclerosis, it is unclear whether this is related to an effect of steroids or is merely a manifestation of more severe disease. It is possible that steroids may provide a protective effect in reducing inflammatory vascular damage (32).

Acute myocardial infarction secondary to vasculitis alone is rare in patients with SLE, although immune complex disposition in the walls of extramural coronary arteries occurs (33). Sudden death because of rupture of an atherosclerotic aortic aneurysm may also occur (34–37).

Endocarditis

Sudden death from endocarditis may result when fragile vegetations embolize to the brain and coronary arteries, but is an uncommon manifestation of SLE. The typical Libman–Sachs endocarditis of SLE is characterized by nonbacterial verrucous deposits on the valvular and endocardial surface and has been found in 40–50% of cases of SLE at autopsy (22). The antiphospholipid syndrome is likely to be associated with this (38).

Neurological Disease

Neurological complications of SLE are common and include psychiatric conditions, stroke, peripheral neuropathies, myositis, transverse myelitis, and epilepsy (39,40).

Epilepsy

Sudden death as a result of epilepsy should be considered in patients with SLE because of their increased risk of developing the disease; for example, a total of 10–35% of patients with SLE experience epileptic seizures, with grand mal episodes being the most common (41).

Individuals with epilepsy have a 24-fold increased risk of sudden unexplained death compared to the general population (42), and Appenzeller et al. (43) have reported details of 519 patients with SLE, with 12% having epileptic seizures. Of note, all showed concordance with antiphospholipid syndrome, which is also thought to be associated with some of the neuropsychiatric manifestations of SLE (6,44).

Cerebrovascular Accidents

Cerebrovascular accidents occur in 5–10% of patients with SLE (41). Ischemic cerebral events are less commonly caused by embolization from Libman–Sachs endocarditis than from atherosclerotic narrowing of vessel with thrombosis associated with small vessel vasculitis, antiphospholipid syndrome, and renal hypertension (39,45). Central nervous system vasculitis is a known cause of sudden unexpected death in patients with SLE (10), which is characterized by inflammation within vessels of the leptomeninges and cerebral parenchyma. The clinical diagnosis is, however, difficult, and there are no laboratory tests to confirm its presence; CT and MRI may reveal microvascular infarctions, calcification, and microhemorrhages. Clinical manifestations noted on history depend on the vessels affected and include seizures, psychosis, and confusion. A history of vasculitis elsewhere may suggest this diagnosis at autopsy (6,10,46).

Cerebral hemorrhage in SLE may be attributed to weakening of the walls of cerebral vessels by arteritis or to cerebral artery aneurysm rupture (41).

Although the most common manifestation of cerebral SLE is psychologic disturbance, a 20-year retrospective cohort study of 300 patients with SLE revealed suicide attempts in 2%, with only one fatality (39,47).

Pulmonary Disease

Acute Pulmonary Hemorrhage

This is a rare manifestation of SLE, but one that may be associated with a high mortality. In an analysis of 32 patients with diffuse alveolar hemorrhage, 19 died (a mortality rate of 59%)—the fatalities including 12 patients with SLE (48). Other studies have demonstrated death rates as high as 90% among patients with SLE (49). Acute pulmonary hemorrhage presents clinically with severe dyspnea with or without hemoptysis (50,51). Sudden and unexpected death has been reported in these patients and is often a result of acute respiratory failure resulting in hypoxia (49,50,52).

Histological examination of areas of alveolar hemorrhage may show either diffuse or focal collections of red blood cells, with or without fibrinoid necrosis, pulmonary capillaritis, and microangiitis, with immune complex disposition (49,53,54). There may also be lung infections and other disease manifestations of SLE, such as pulmonary fibrosis, antiphospholipid syndrome, and nephritis, that also increase the risk of mortality (48–50,52,55). Zamora et al. (49) reported a 94% concordance (14 of 15 patients) between diffuse pulmonary hemorrhage and lupus nephritis.

Pulmonary Hypertension

This may arise secondary to pulmonary embolism, vasculitis, and lung fibrosis leading to cor pulmonale that can be a cause of sudden death from arrhythmia (51,56). Between 5% and 14% of patients with SLE have pulmonary hypertension (51).

Pneumothoraces

The occurrence of pneumothorax in patients with SLE is rare; however, bilateral recurrent pneumothorax may result in death. Autopsy studies have shown a large number of subpleural bullae associated with interstitial fibrosis (51). Imaging or testing at autopsy will be required to identify this possibility.

Gastrointestinal Disease

Gastrointestinal manifestations of SLE are common, but do not usually result in sudden or unexpected death. However, intestinal ulceration and acute pancreatitis may both have rapidly lethal consequences (56–59). Mesenteric vasculitis may have a high mortality if not recognized and treated promptly and has been reported in up to 60% of patients with SLE who have presented with abdominal pain. The overall prevalence of the condition in SLE is, however, low ranging from 0.2% to 1.1% (60). Death may occur from necrosis, ulceration, and perforation of the intestine with rapidly progressing septicemia (58). Mesenteric ischemia may also occur in patients with SLE because of the increased risk of atherosclerosis and thromboembolism (60) again leading to mesenteric vascular insufficiency, infarction, perforation, and death. A study by Breuer et al. (61) revealed that the incidence of acute pancreatitis in SLE ranges from 0.4 to 1.1 per 1000 patients, with a mortality rate 27% higher than the general population. The autopsy findings include vasculitis, thrombosis, intimal proliferation, and necrosis.

Sepsis

Sepsis is a common cause of death in patients with SLE, with approximately 30% of European patients with SLE dying from infections; lethal outcomes can be correlated with both disease activity and immunosuppressive treatment (3,62). In a recent study of 5335 patients with SLE, the mortality rate because of infection was 4.7% (63). Infections included bacteria, viruses, and fungi and resulted in rapid death because of impaired immune responses, genetic immune abnormalities, and associated comorbidities (12). Infections tended to arise from pulmonary, abdominal, and urinary sources (3).

Bacterial organisms that are most often responsible for fatalities include *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Salmonella enteritidis*, and *Salmonella typhimurium*. Multiresistant nosocomial infections are often because of *Pseudomonas aeruginosa*. Other opportunistic infections with a high mortality include *Pneumocystis jiroveci*, candida, aspergillosis, *Mycoplasma avium*, *Mycoplasma kansasii,* and *Mycoplasma tuberculosis*. *Listeria monocytogenes* is an uncommon cause of meningitis that may be found in patients with SLE (12). A study of acute viral infections revealed that death in patients with SLE was most often caused by acute infection with CMV, herpes simplex virus, EBV, and varicella zoster virus (64). Given the susceptibility of individuals with SLE to sepsis from a variety of organisms, a full microbiological work up should be carried out at autopsy to screen for possible pathogenic organisms.

Renal Disease

Hypertension is an important risk factor for cardiovascular events in patients with SLE (29), and women with SLE are more likely to have hypertension compared to the general population (65). The underlying mechanisms for this are not well understood, but are associated with a high incidence of renal disease and antiphospholipid syndrome.

Lupus nephritis is the broad term used to describe kidney disease in SLE, with glomerulonephritis and nephrotic syndrome being two frequent manifestations. It is one of the most common presentations of SLE, with up to 80% of affected individuals developing this complication with resultant hypertension. For example, Nezhad and Sepaskhah (66) reported that approximately 61% of their patients with lupus nephritis were hypertensive at the stage of renal biopsy.

Antiphospholipid syndrome can also contribute to the increased incidence of hypertension and impaired renal function in patients with SLE by inducing renal vascular hypertension, although the exact role remains uncertain. Renal vascular lesions, such as thrombotic microangiopathy and fibrous intimal hyperplasia, can also lead to renal artery stenosis and increased renin-angiotensin system activation with resultant hypertension (67).

Prolonged hypertension increases the risk of stroke and left ventricular hypertrophy and thus of sudden death in affected individuals (68). In a study of 157 Taiwanese patients with pediatric SLE, 33.8% were shown to have cardiomegaly on echocardiography (69). Pieretti et al. (70) also reported a significant increase in the prevalence of left ventricular hypertrophy among hypertensive patients with SLE compared to hypertensive patients without SLE, thus indicating that SLE is an independent risk factor for left ventricular hypertrophy.

Miscellaneous

The antiphospholipid syndrome refers to an autoimmune disorder characterized by multifocal vascular thromboses and/or

pregnancy-related morbidity associated with persistently elevated antiphospholipid antibodies (lupus anticoagulant test, anticardiolipin antibodies, and/or anti-β2-glycoprotein I antibodies; [71]. Although it may develop in well individuals, it may also occur in association with SLE. Clinical manifestations include cerebrovascular events, deep venous thromboses (with or without pulmonary thromboembolism), myocardial infarction, and pulmonary hypertension (11,45,55). The involved antibodies bind prothrombin, glycoproteins, and protein/phospholipid complexes leading to a hypercoagulable state (53). Antiphospholipid antibodies are present in 30–50% of patients with SLE (30), with antiphospholipid syndrome developing in 50–70% of those who harbor the autoantibody, increasing their risk of developing these life-threatening conditions (11). Rarely, the catastrophic antiphospholipid syndrome may develop where there are widespread thromboses with microangiopathic hemolytic anemia and multiorgan failure. Adrenal gland infarction may result in acute adrenal insufficiency (71).

Conclusion

SLE is a complex disorder that involves many organ systems with very varied clinical manifestations. Because of this complexity, it is often difficult to understand the range of manifestations that may be present at autopsy and to determine what relationship the autopsy findings might have to the terminal lethal mechanisms. This review provides an outline of the characteristic features of SLE that may play a role in sudden and/or unexpected death and focuses on specific features that should be evaluated at the time of postmortem dissection. Given that many of the manifestations of SLE may be quite subtle macroscopically, careful histological sampling and evaluation of suspected cases is required.

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