Autoimmune Connective Tissue Diseases: Systemic Lupus Erythematosus and Rheumatoid Arthritis

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KEYWORDS

• Rheumatologic emergencies • Systemic lupus erythematosus • Rheumatoid arthritis • Therapy • Adverse reactions

KEY POINTS

- Signs and/or symptoms considered rheumatic in origin may account for a significant proportion of emergency department visits.
- Absolute or true life- and/or limb-threatening complications associated with autoimmune connective tissue diseases are rare.
- Failing to consider such a diagnosis by virtue of cognitive error, such as availability, may have catastrophic consequences for the patient.
- Underlying stressors and/or concomitant acute or worsening chronic diseases in need of targeted intervention, if left untreated, may contribute to the demise of the patient.
- Patients receiving treatment for autoimmune connective tissue diseases are vulnerable to adverse drug reactions and complications attributable to the deleterious effects of such medications, which can vary widely in their severity, from the mild to lethal.

INTRODUCTION

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are just 2 of several autoimmune connective tissue diseases that are primarily chronic in nature but can present to the emergency department by virtue of an acute exacerbation of disease. Beyond an acute exacerbation of disease, their predilection for invading multiple organ systems lends itself to the potential for patients presenting to the emergency department with either a single or isolated symptom or a myriad of signs and/or symptoms indicative of a degree of disease complexity and possibly severity that warrants as timely recognition as it does resuscitation.

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As many as nearly 9% of all patients presenting to the emergency department do so with symptoms consistent with rheumatic disease.[1] The most common symptoms patients may experience are constitutional, such as fever, fatigue, and weight loss, and musculoskeletal such as neck, back, and/or joint pain and swelling. In general, purely nontraumatic musculoskeletal symptoms account for up to 3% of all patients presenting to the emergency department, approximately 57% of which are back pain related, while approximately 43% are related to a peripheral joint, with 0.6% and 0.3% of these, respectively, being emergent in nature.[2] Beyond the constitutional and musculoskeletal symptoms that may trigger an emergency department visit, the multiorgan system propensity of these conditions yields symptoms that run the gamut of patient experience, the most emergent of which tend to be airway related, cardiovascular, gastrointestinal, hematopoietic, infectious disease, neurologic, pulmonary, and/or renal.

An awareness of autoimmune connective tissues diseases and more specifically the emergent manifestation of their potential presentations is vitally important to the timely recognition of disease states in need of specific, targeted, aggressive intervention that is often multifaceted and multidisciplinary in its approach. Such awareness affords one the opportunity to make the time-sensitive critical decisions that are required to ensure the best possible clinical outcome.

EPIDEMIOLOGY

Both SLE and RA possess a predilection for women. They share a female-to-male ratio of 3:1, but this is only the case in childhood as it relates to SLE, at which time disease tends to be much more severe.[3] During the course of their reproductive years, women are affected by SLE anywhere from 7 to 15 times more often than men, with a median age of onset of 37 to 50 years and 15 to 44 years for white and Black women, respectively and 50 to 59 years and 45 to 64 years for white and Black men, respectively.[4,5] In general, older adults tend to experience a much milder form of disease but men, who are typically older at the time of onset, tend to have a worse outcome with a higher incidence of hematologic, cardiovascular, neurologic, and renal disease and vasculitis among other complicating features.[6–8]

RA tends to affect an older patient population, with a peak incidence in the eighth decade of life, but like SLE, women are oftentimes affected during the latter part of their childbearing years. Unlike SLE, for which, a greater prevalence of disease is found in Asians, African Americans, African Caribbeans and Hispanic Americans, RA has a greater prevalence among Western Europeans and North Americans (Caucasians) and Native Americans.[9–11]

Increased risk associated with SLE and RA has been attributed to lower socioeconomic status[12,13] and education,[14,15] obesity,[16,17] and cigarette smoking.[18,19] The increased morbidity and mortality associated with such socioeconomic, comorbid, and environmental conditions suggests that modifiable risk factor reduction and an improvement in access to medical care may dramatically impact the clinical course of disease for many patients.

PATHOPHYSIOLOGY

SLE and RA are 2 of several autoimmune connective tissue diseases that wreak havoc on one's own self because of a loss of self-tolerance. The identification of self as a threat triggers an immune response, both innate and adaptive, ultimately as dysfunctional as it is destructive, aimed at eliminating the threat by any and all means necessary. The pathogenesis of SLE, like RA, is multifactorial.[20]

Genetic, environmental, immunoregulatory, hormonal, and even epigenetic factors trigger a series of events or events in parallel that promote both B- and T-cell activation. The resultant production of autoantibodies, cytokines and immune complexes, which when deposited in the tissues of target organs, causes local inflammatory destruction via activation of the complement cascade. The damaged tissue of target organs liberates apoptotic cells that when defectively cleared present novel autoantigens. These novel autoantigens when bound to autoantibodies form immune complexes supporting further priming and autoreactivity in a cycle that if left uninterrupted ultimately and irreparably destroys organ systems.[21,22]

EMERGENCY MANIFESTATIONS OF DISEASE

Emergencies in patients with autoimmune connective tissue diseases generally fall into 1 of 5 distinct categories: exacerbations of the diseases themselves, complications known to be associated with the autoimmune connective tissue disease, infections attributable to immunosuppressive therapy, new onset or an exacerbation of a comorbid condition, and adverse drug reactions related to the medications used to treat such conditions.[23] It is important to recognize the potential for not only an acute exacerbation of disease but also a complication of the same in a patient who has not yet had such a diagnosis established in the outpatient setting. Their presentation to the emergency department may be the first disease-related illness of significant enough acuity to warrant emergent medical attention.

AIRWAY-RELATED EMERGENCIES

The potential for life-threatening complications associated with airway-related emergencies in SLE and RA is not limited to acute catastrophic conditions caused by these systemic rheumatic diseases.

Pathologic changes in anatomy create scenarios in which a routine approach to the process of securing an airway in these patients can be fraught with danger and vulnerable to failure. An awareness of these potential procedurally related challenges ensures a level of preparedness including the consideration of alternative, adjunctive techniques and equipment that may prove pivotal in outcome in an emergent situation.

Upper airway obstruction is a potential complication of SLE and RA. Both conditions are associated with cricoarytenoid arthritis but differ in its onset. Acute cricoarytenoid arthritis is a rare but serious cause of upper airway obstruction in patients with SLE. It can be seen in isolation or complicated by secondary bacterial infection such as with epiglottitis or tracheitis. Typical symptoms are to be expected, such as pain in the throat that is exacerbated by speaking and/or swallowing, a sense of fullness or foreign body, change in the sound of speech, shortness of breath, and even stridor. When it occurs, it typically does so in the presence of other associated symptoms and is treated with high-dose corticosteroids, racemic epinephrine, and if indicated, antibiotics. In contrast, chronic cricoarytenoid arthritis is seen in RA and often requires surgical intervention.[24] Although chronic in nature, when associated with laryngeal manipulation or infection, it too can prove acutely fatal.

In a patient with systemic rheumatic disease, a compromised airway, in need of being secured, can prove to be challenging. Temporomandibular joint dysfunction in the setting of RA can significantly reduce opening of the mouth, limiting one's view of the relevant anatomy required for intubation.[23] RA most often affects the cervical spine and in the form of atlantoaxial instability with C1- C2 subluxation or dislocation. Presentation can appear as seemingly mild and benign as being purely radicular in nature

but may in fact be caused by myelopathy or as severe as to cause sudden death.[25] Atlantoaxial instability with C1-C2 subluxation or dislocation must be considered in the differential diagnosis for any patient presenting with upper extremity radicular symptoms and/or new occipital pain. A pre-existing diagnosis of RA certainly helps but is not always established, and as consequence, a high index of suspicion is essential. Patients with known RA with or without confirmed atlantoaxial instability with C1-C2 subluxation or dislocation must avoid hyperextension of the cervical spine and maximal passive flexion, which is particularly important to remember when examining a patient after blunt trauma and when positioning a patient for intubation.[26]

At the bedside and beyond, the equipment required for direct laryngoscopy and additional equipment to assist in securing the airway via video laryngoscopy or fiberoptic intubation should be available. In all instances, the possibility of having to resort to a surgical approach must be considered. At the bedside, the equipment necessary to perform a cricothyroidotomy is required, and if appropriate, transfer to the operating room should be considered in patients for whom intubation is anticipated but not immediately necessary.

CARDIOVASCULAR EMERGENCIES

Patients with SLE and RA are vulnerable to the same traditional risk factors for cardiovascular disease (CVD) as those without either of the 2 systemic rheumatic diseases. They are, however, at greater risk overall because of the pathophysiologic mechanisms associated with these conditions and some of the therapeutic agents used to treat them, enabling accelerated atherosclerosis and as a consequence, CVD at a much younger age than the traditional patient. The risk for patients with SLE is at least twice that of the general population, with an acute myocardial infarction (AMI) relative risk of 2.27.[27,28] Patients with RA have an increased risk of acute coronary syndrome (ACS) demonstrated by an overall hazard ratio of 1.41 when compared with the general population.[29] Cardiovascular emergency in the form of ACS secondary to accelerated atherosclerosis in the setting of SLE and RA is by no means the only potential for disaster. Diseases of the electrical conducting system, myocardium, pericardium, valves, and vasculature also have the potential to wreak havoc and in some instances just as or even more lethally.

Arrhythmias are common in SLE and RA and while the most common of these, sinus tachycardia, is typically benign (present in up to 18% of patients with SLE), some can be malignant.[30] High-degree atrioventricular (AV) block, while rare, in the setting of RA is usually complete.[31] Atrial fibrillation is seen in 9% of patients with SLE, and patients with RA have a 40% greater risk of atrial fibrillation than the general population.[30,32] QT prolongation is seen in 17% of patients, increasing the risk for ventricular tachyarrhythmias and as a consequence sudden cardiac death.[30]

Cardiac complications are reported in about 50% of patients with SLE and RA, the most common of which is pericarditis.[31,33] Typically, pericarditis does not occur in isolation but instead with other forms of serositis. More often than not pericarditis is either entirely asymptomatic or benign but can be complicated by pericardial effusion and tamponade and/or be constrictive in its form and as a consequence function impairing cardiac output potentially to the point of collapse.

Myocardial dysfunction to the point of failure is observed in both SLE and RA, the etiology of which is varied. Congestive heart failure may be the direct result of that which has been mentioned previously but may also result from additional cardiac complications associated with SLE and RA such as myocarditis (often with pericarditis), cardiomyopathy, and valvular disease, be it thickening of valve leaflets

associated with episodes of valvulitis or endocarditis. Regardless of the cause of valvular disease, it is typically left-sided and regurgitant.[34,35]

Aortic disease, in the form of root abnormality, aortitis, and/or aneurysm, although rare, is more commonly seen in patients with SLE and RA than in the general population.[36] In its most potentially lethal form and via multivariate analyses, patients with SLE and RA have been found to have odds ratios of 2.06 and 1.406 respectively, associating SLE and RA with the coexistence of aortic aneurysms at a significantly higher rate than that seen in the general population.[37,38]

Beyond aortic aneurysm with dissection and/or rupture, thromboembolism is a major cause of morbidity and mortality for patients with rheumatic disease and in particular SLE and RA. All vessels, big and small, arterial and venous, end organ and extremity, are vulnerable. The potential for loss of limb because of peripheral artery ischemia or life because of such potentially catastrophic events as cavernous sinus thrombosis (CST), cerebrovascular accident (CVA), ACS, pulmonary embolism (PE), and the like is much greater than the general population.[39] In some instances, rates of disease, such as venous thromboembolism, are more than 3 times higher than the general population.[40]

In isolation, any organ system compromised by thromboembolism can prove fatal but when multiple organ systems are involved, such as that which occurs in the setting of catastrophic antiphospholipid syndrome (CAPS), half of all patients will die regardless of resuscitative efforts.[41] CAPS is exceedingly rare, representing less than 1% of all patients with APS but is its most severe and rapidly progressing form that in less than 10% of cases is associated with concomitant disease such as SLE and RA, requiring a high index of suspicion. Although absolute confirmation of the diagnosis is beyond the emergency department, requiring an element of histopathological and/or laboratory confirmation, evidence of 3 or more compromised organs, systems, and/or tissues, all having manifested simultaneously or in less than 1 week, in a patient with SLE or RA is highly suspicious.[42] The organ systems involved in decreasing order of frequency include renal (78%), pulmonary (66%), central nervous system (56%), cutaneous (50%), gastrointestinal (38%), hepatic (34%), adrenal (13%), and urogenital (6%).[41]

Once suspected, treatment is to be initiated early and aggressively. Multidisciplinary in its approach, access, ventilatory support, monitoring, fluid resuscitation, electrolyte balance, anticoagulation, and high-dose glucocorticoids are the mainstays of treatment. If these are ineffective, cyclophosphamide and gamma globulin are recommended, and finally, if all else fails, plasmapheresis.[43] Primary as these interventions are in their approach, additional treatment must also be considered in the setting of any underlying or inciting secondary stressor such as antibiotics for infection or operative intervention in the face of organ or extremity necrosis.

GASTROINTESTINAL EMERGENCIES

Both SLE and RA can affect the gastrointestinal (GI) system, with up to 50% of patients with SLE manifesting some form of GI symptomatology during their lifetime; however, actual GI emergencies are rare.[44] Like any other organ system, the GI tract, both hollow and solid, is vulnerable to the same inflammatory and vaso-occlusive dangers associated with SLE and RA and complications associated with their treatment. When caused by the pathophysiologic mechanisms associated with these conditions, most cases can be life threatening if not recognized and treated promptly.[45] Ischemia, infarction, perforation, and end organ failure are on a spectrum of disease carrying a high rate of morbidity and/or mortality. When caused by mesenteric vasculitis,

mortality rates are as high as 13%.[46] Prompt administration of glucocorticoids is essential and in refractory cases immunosuppressive agents and biologic agents may be required.[47] Beyond the systemic rheumatic diseases themselves, agents used to treat them, namely glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs have been implicated in GI perforations.[48] Regardless of etiology, be it medication or directly disease related, evidence of perforation or end organ compromise including necrosis warrants operative intervention and should not be delayed.[49]

HEMATOPOIETIC EMERGENCIES

Patients with SLE and RA are prone to several hematological disorders, either as a direct consequence of the diseases themselves or the therapeutic agents used to treat them. Of course, one must always consider the possibility of an alternative etiology for the same abnormalities such as infection, malignancy, or some other secondary stressor. In most instances, the hematological findings are nonemergent in nature such as anemia of chronic disease, the most common hematological disorder in SLE and among the most prevalent in RA.[50,51] In rare instances, hematologic emergencies do occur and if unrecognized can prove fatal.

Accelerated loss caused by bleeding, hemolysis, or hypersplenism are potential causes of severe anemia that in the setting of systemic rheumatic disease may not be as simple to address via transfusion alone. Even in the absence of loss, hemolysis, or hypersplenism, severe anemia may occur because of autoimmune bone marrow suppression or may be medication induced. Although bleeding is a risk for patients because of coagulation abnormalities, so too is clotting, as is the case with thrombotic microangiopathies such as CAPS described previously and thrombotic thrombocytopenic purpura. Mortality associated with these conditions is exceedingly high and can be rapid. Approximately 50% of patients with CAPS will die regardless of intervention, and the same percentage of patients with thrombotic thrombocytopenic purpura (TTP) associated with SLE will die if it is not recognized early and treated aggressively via plasma exchange and immunosuppression.[41,52] If untreated, mortality rates approach 90%, and even with aggressive intervention can still be as high as 25%.[53] Delays in initiating plasma exchange increases mortality, furthering the need for early recognition and resuscitation requiring an urgent multidisciplinary approach.[54]

INFECTIOUS DISEASE EMERGENCIES

Any immunocompromising condition, any immunosuppressing treatment, places patients at increased risk of not only serious infection but also its associated increased risk of morbidity and mortality.

Infections are common in patients with systemic rheumatic disease, and the more active the disease, the more serious is the infection, at times yielding a mortality rate that even matches the disease itself.[55] Patients with systemic rheumatic disease are more vulnerable to infections by certain types of pathogens, be they encapsulated, opportunistic or not, but they are still most commonly infected by the same organisms found in the general population, primarily impacting the respiratory and urinary tracts and skin.[56] It is also important to keep in mind that although an acute exacerbation of disease might yield findings consistent with the systemic inflammatory response syndrome not caused by infection, empiric antibiotics are recommended until infection as an etiology of these findings has been ruled out.

Although pulmonary, genitourinary and dermatologic infections are common to both SLE and RA, as they are in the general population, septic arthritis is not as frequently

observed in patients with SLE as it is in RA, occurring in less than 1% of hospitalized patients.[57] It is, however, just as dangerous, rapidly leading to joint destruction, quite possibly systemic infection, loss of limb, and possibly life, requiring a high index of suspicion and the prompt initiation of antibiotic treatment following arthrocentesis.[58] Abnormal joint architecture as seen in patients with RA is the most important risk factor, with the therapeutic agents used to treat the disease, in particular glucocorticoids and biologic agents only further increasing this risk.[41,59] It is especially important to recognize that patients actively being treated with such agents are not only more vulnerable because of immunosuppression, but they also might not manifest signs and/or symptoms as intense as those not receiving such treatment.

NEUROLOGIC EMERGENCIES

Although rare, neurologic emergencies, like many other potential threats in SLE and RA, are much more frequently encountered than they are in the general population. As a consequence, there is increased risk because of the pathophysiologic proinflammatory, vaso-occlusive, and coagulopathic nature of these systemic rheumatic diseases and the complications associated with the therapeutic agents used to treat them. An example of this increased risk is observed in patients with SLE who have a two to ten-fold increase in the risk of CVA, with patients less than 50 years of age at greatest risk.[60] Not only are patients at increased risk of CVA, the severity of the event itself tends to be much greater, resulting in not just greater mortality but also morbidity.[61] Vascular catastrophe, be it because of increased risk of thrombosis, embolism, hemorrhage, vasculitis, or dissection, is not the only potential for neurologic disaster; so too is mechanical catastrophe, such as that which occurs in the setting of RA and its associated degenerative disease of the cervical spine, and instability of the atlantoaxial joint and its propensity for subluxation or dislocation as discussed previously. Patients with SLE and RA are at significantly increased risk of sudden death in the setting of either situation.[25,28] These are of course not the only potential threats.

The proinflammatory danger of disease cannot be overstated. Neurologic emergencies such as central nervous system (CNS) vasculitis and transverse myelitis must be considered in the differential diagnosis of any patient presenting with manifestations of neurologic disease, be it brain or cord consistent. The potential for significant morbidity from loss of function and mortality is great, requiring the initiation of early and aggressive treatment including glucocorticoids, immunosuppressive agents, and possibly plasmapheresis.[62]

Timely intervention is, however, not the only concern; so too is possible complication associated with failing to have considered a diagnosis such as cerebral vasculitis as an etiology for a patient's stroke-like presentation or an etiology of Libman-Sacks endocarditis with its associated emboli as a cause of CVA, an absolute contraindication to the administration of tissue plasminogen activator (tPA). Although not an established contraindication, caution must be taken in the setting of CNS vasculitis, as thrombolysis could prove disastrous because of an increased risk of hemorrhage.[63]

PULMONARY EMERGENCIES

As is the case with other organ systems, pulmonary disease in the setting of SLE and RA may be a function of the pathophysiologic nature of the diseases themselves or as a consequence of the therapeutic agents used to treat them. Anatomic changes to the lungs over time yielding interstitial lung disease and pulmonary hypertension, acute events such as thromboembolism or hemorrhage, and infections and comorbidities

all contribute to increased morbidity and mortality, with each only further increasing the risk for another. Although pulmonary disease is common in systemic rheumatic disease, acute life-threatening catastrophic pulmonary events are rare; 2 of the most lethal are diffuse alveolar hemorrhage (DAH) and lupus pneumonitis.

Both lupus pneumonitis and DAH are associated with high rates of mortality, approximately 40% and 25%, respectively.[64–66] Patients are typically ill appearing with signs, symptoms, and diagnostic findings seemingly consistent with pneumonia. Disease progression is rapid, often culminating in respiratory failure in need of intubation and mechanical ventilation, an outcome that according to 1 study related to DAH was met with a mortality rate of 62% versus a rate of 0% for patients not requiring such intervention.[67] A firm diagnosis of lupus pneumonitis or DAH is beyond the emergency department, where the primary responsibility is to resuscitate and rule out other potential emergent etiologies for the patient's presentation. Although confirmatory diagnosis is beyond the emergency department, timely diagnosis is essential, as any delay in the administration of glucocorticoids and immunosuppressive therapy such as cyclophosphamide only worsens prognosis.[65]

RENAL EMERGENCIES

Like other organ systems, renal impairment is relatively common in systemic rheumatic disease. Lupus nephritis is present in up to 38% of patients with SLE at the time of initial diagnosis and ultimately impacts up to 50% of patients.[68,69] Although actual emergencies are rare, renal disease is a significant contributor to morbidity and mortality, both chronically and acutely, with 10% to 20% of patients progressing to end-stage renal disease and up to 42.2% of admissions to the intensive care unit (ICU) caused by acute kidney injury.[68,70] Renal impairment in RA is less frequent with the use of methotrexate and newer biologic disease-modifying antirheumatic drugs achieving better control over systemic inflammation and reducing the need for NSAIDs.[71] Acute renal failure is still a potentially dangerous situation for patients with SLE and RA, whether it is caused by flare, vaso-occlusive crisis such as that which occurs in the setting of CAPS, or as an adverse effect of the therapeutic agents used to treat the diseases.

ADVERSE DRUG REACTIONS

Patients with SLE and RA are vulnerable not only to acute exacerbations of the diseases themselves and their associated complications but also adverse drug reactions related to the therapeutic agents used to treat them, which can range from mild to severe and even life-threatening. Although the majority of adverse drug reactions are classified as mild or moderate, 36.6% and 40.7% respectively, 22.7% are classified as severe.[72] Glucocorticoids and disease-modifying antirheumatic drugs are associated with a litany of potentially major adverse drug reactions.[23,73] Major adverse drug reactions associated with glucocorticoids include but are not limited to those that are:

- Ophthalmologic (elevated intraocular pressure)
- Cardiovascular (hypertension, arrhythmias, premature arteriosclerosis)
- GI (peptic ulcer disease, visceral perforation)
- Musculoskeletal (osteoporosis, avascular necrosis)
- Neuropsychiatric (depression, psychosis)
- Metabolic (hyperglycemia, hypothalamic-pituitary-adrenal insufficiency)
- Immune system related (increased risk of infections)

Major adverse drug reactions associated with disease-modifying antirheumatic drugs include but are not limited to anaphylaxis, anemia, leukopenia, thrombocytopenia, and immunosuppression. Patients are susceptible to a host of infections, among them bacterial, fungal, and viral, some newly acquired, others reactivated, and some even opportunistic.

DISCLOSURES

The author has nothing to disclose.

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