Munther A. Khamashta
Manuel Ramos-Casals *Editors*

Autoimmune Diseases

Acute and Complex Situations

Springer

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(Editors)

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This book is dedicated to the memory of our friend and inspirational leader, Dr. Josep Font.

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Assessment and Management of the Rheumatological Patient in the Critical Care Unit

1

David P. D'Cruz and Duncan L.A. Wyncoll

Abstract Musculoskeletal diseases are common and may result in significant morbidity and mortality especially in the context of the multisystem autoimmune rheumatic disorders. Patients with rheumatological disorders present acutely to emergency rooms, and the cause of the sudden deterioration may be due to complications of the underlying disorder, sepsis, or an iatrogenic effect resulting from an acute adverse event from therapy. Given the complexity of these patients, it is not surprising that outcome can be poor with in-hospital mortality rates of 40%. This introductory chapter is aimed at the admitting physician presented with an acutely ill patient with a rheumatological disorder who is deteriorating rapidly and needs admission to a critical care unit.

Keywords Critical care assessment and management • Immunosuppression • Multiorgan failure • Multisystem autoimmune rheumatic disorders • Sepsis

1.1 Introduction

Musculoskeletal diseases are common in the community and represent a major health care burden. These disorders may result in significant morbidity and mortality especially in the context of the less common multisystem autoimmune connective tissue disorders. From the patient's perspective, the risk of disability, economic loss because of inability to work and consequent dependence on benefits, poor quality of life, and loss of confidence and self-esteem can be life-changing.

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While many of the musculoskeletal disorders including degenerative diseases, such as osteoarthritis, are associated with the normal aging process, some of these conditions will reduce life expectancy. For example, many of the inflammatory arthropathies are associated with an increased risk of premature mortality from cardiovascular disease. In other conditions such as systemic lupus erythematosus and the systemic vasculitides, renal disease and infections associated with immunosuppression are common causes of death.

There has been a revolution in the treatment of the inflammatory arthropathies. A decade or two ago, there were few effective treatments, and these were only used when nonsteroidal anti-inflammatory drugs had failed. The modern approach is to aim for an early diagnosis and to commence disease-modifying therapy immediately in order to prevent damage and disability. However, immunosuppressive agents and the biologics are extremely effective therapies but carry a significant burden of toxicity.

Patients with rheumatological disorders present acutely to emergency rooms, and the cause of the sudden deterioration may be due to complications of the underlying disorder, sepsis, or an iatrogenic effect resulting from an acute adverse event from therapy. Rheumatoid arthritis is the most common rheumatic disease seen in critical care units, followed by systemic lupus erythematosus and scleroderma, and these three conditions may account for up to 75% of patients with rheumatic disorders admitted to critical care services.[1] Given the complexity of these patients, it is perhaps not surprising that outcome can be poor with in-hospital mortality rates of 30–40% or more.[2]

This introductory chapter is aimed at the admitting physician presented with an acutely ill patient with a rheumatological disorder who is deteriorating rapidly and needs admission to a critical care unit. There have been major advances in the care of critically ill patients, including the way critical care units are run, moving from the previous "open" model of care to a "closed" system of multidisciplinary care and these will also be reviewed.

1.2 Initial Assessment of the Acutely Ill Patient

Early recognition that a patient's condition is deteriorating is essential, and in those patients who are severely unwell, immediate action is frequently required to correct abnormal physiology before a full history and examination can be carried out. If appropriate action is delayed, then there is a risk of further damage to vital organs, such as the brain and kidneys. Increasingly, it is being recognized that most in-hospital cardiorespiratory arrests are preventable if timely decision making is made, and relatively simple interventions such as antibiotics, fluids, oxygen administration, vasopressors, and appropriate intubation were carried out earlier.

Clinical severity may be obvious from the end of the bed, such as in a patient who presents with a massive pulmonary embolus, or a cerebral hemorrhage. In this situation, organ damage may well have occurred, but prompt intervention gives the best chance of recovery and prevents further secondary organ damage. Progressive insidious deterioration is less easy to spot, and often the hardest decision for an acute physician is to determine the precise point at which to refer a patient to critical care. Currently, the best approach is to

monitor the basic physiological variables (respiratory and heart rate, blood pressure, urine output, oxygen saturation, and conscious level), and then by using a scoring system, agreed levels for referral to a "patient-at-risk," "outreach" or "medical emergency" team can be locally determined – these are often known as "Track and Trigger" systems. Around the world, use of these scoring systems, allied with support teams has been shown to expedite admission to critical care facilities and to prevent unnecessary in-hospital cardiac arrests.

Critical care units should no longer be viewed upon as "ventilation units," but should be utilized as the best places to take patients who are at high-risk of deterioration, since all the expertise and equipment is available "on tap" in a specifically designed location.

Initial assessment of the acutely unwell patient should be systematic, and the ABCD approach is a useful tool:

- **A**irway
- **B**reathing
- **C**irculation
- **D**isability

Airway obstruction (partial or complete) is a medical emergency leading to hypoxia, coma, and death within a few minutes if left uncorrected. It can result from aspiration, edema, bronchospasm, or most commonly reduced upper airway tone in patients who are obtunded. Simple airway maneuvers such as head tilt and chin lift, or a jaw thrust are usually effective; suction can remove blood, vomit, or foreign bodies. Intubation should be undertaken if the precipitant is unlikely to be resolved speedily.

The respiratory rate (<8 or >25/min) is widely thought of as the most sensitive marker of a deteriorating patient; central cyanosis and a fall in oxygen saturations may occur late. Oxygen should be administered early, and a clinical assessment made of the respiratory system. If time allows, arterial blood gas analysis and a chest radiograph can help determine further management. Traditionally, textbooks have given levels of PaO_2 and $PaCO_2$ that are absolute indications for ventilatory support (either invasive or noninvasive), but increasingly, these are not relied upon, and referral to a critical care specialist for an opinion is advised.

Hypovolemia and a low cardiac output are extremely common in acutely unwell patients. The heart rate is often falsely low because of medication (e.g., beta-blockers or digoxin), and many patients compensate well initially with increased peripheral resistance. Significant hypovolemia is relatively easy to detect, but occult hypovolemia (of up to 20%) is frequently overlooked. A mild metabolic acidosis and a raised lactate (>1.6 mmol/L), with cool peripheries and a prolonged capillary refill time, suggest the need for urgent intravenous fluids. A challenge of at least 20 mL/kg of a balanced crystalloid (such as Hartmann's) over 30–60 min is the best start, unless there is obvious heart failure. Further fluid resuscitation can be determined after response to the initial challenge, and after placement of a urinary catheter.

The neurological status can be rapidly determined by the Glasgow Coma Scale (GCS). In those who have a decreased conscious level, an early CT scan of the brain is indicated. Again, practice has changed in recent years, with patients being intubated for airway protection at less severely abnormal levels of consciousness, rather than waiting until the GCS is ≤8. Earlier intubation allows clear imaging, and prevents complications such as seizures

and aspiration pneumonia occurring in a dark CT scanning suite. Hypoglycemia and drug intoxication should also be considered as well as ischemia and cerebral infection.

A thorough history and a fuller patient assessment can then be undertaken once stability has been achieved. Further information often then comes to light, as trends in measured physiological parameters are much more useful than single static measurements. Other investigations can then be prioritized, and a plan should be communicated to the whole team.

The management of acutely unwell patients, especially those with rheumatological conditions, frequently involves many teams, such as intensive care, nephrology, hematology, cardiology, respiratory, gastroenterology, and neurology. The outcome is likely to be optimal when these teams work together in a seamless process and cooperate and communicate well. As in all aspects of medicine, strong clinical leadership is an essential component of good team working.

There are two main systems/models of care that are used in critical care units throughout the world – these are known as "open" and "closed." In an open unit, each specialist can give patient care directions, order investigations, and prescribe new treatments for a patient. In a closed unit, specialists continue to visit frequently, but all recommended aspects of care by the different specialists who are consulting are authorized/signed-off by the attending intensive care specialist. The closed model has been shown to better control costs, and results in significantly better patient outcomes. This is perhaps most relevant for extremely complex patients who have multisystem involvement where recommended therapies for one organ may have a detrimental effect on a different system. Intensive care specialists often have significant expertise in understanding physiology and pharmacology as it relates to critically ill patients – especially those with multiple organ failure.

1.3 Specific Assessments of the Critically Ill Rheumatological Patient

It is vitally important to evaluate the rheumatological patient with multiorgan disease with a detailed history and physical examination as these patients often have complex medical problems and are on multiple medications. A referral letter from the primary care physician, if written well, can save much time in the emergency room. It is obviously helpful if the patient is already known to the hospital and the previous records are available and these should provide useful information on the diagnosis and current treatments. Previous investigations if available are especially helpful in terms of looking for changes in radiological appearances, biochemistry, hematology and acute phase markers.

The patient is often able to give a detailed account of the onset of their symptoms. Patients with chronic conditions such as inflammatory arthritis, lupus or systemic vasculitis can often tell the clinician whether the current symptoms represent a flare of the underlying condition, whether there are complications such as infection, or if the presentation represents new or a recurrence of organ involvement such as glomerulonephritis, pulmonary hemorrhage, or a thrombotic manifestation. The patient may also inform the admitting clinician if any new therapies have recently been commenced that may have resulted in a serious adverse effect. If a detailed history from the patient is not possible because

they are too unwell, every effort should be made to speak to any accompanying relatives for as much information on the history as possible, assuming that the patient is able to give consent for the relatives to speak on their behalf.

When the patient has been referred from another hospital, a phone call or e-mail to the referring clinician may give a lot more information than a referral letter. In the age of electronic media, it is often possible for data on imaging studies, for example, to be sent directly between hospitals, reducing the need for unnecessary repetition of imaging, reducing radiation exposure, and giving a baseline for comparison with further imaging studies.

Once the patient has been stabilized as described above, a thorough history should be obtained followed by a detailed examination of all organ systems to rapidly prioritize the most seriously affected organs. During the examination, a careful assessment of all areas of the body is important. Close attention to the hands may, for example, reveal multiple splinter hemorrhages, which could point toward bacterial endocarditis, systemic lupus erythematosus, systemic vasculitis, or antiphospholipid syndrome. Cutaneous vasculitis can range from subtle periungual and digital infarction through to widespread palpable purpura and severe necrotizing ulceration. Livedo reticularis, especially if it is widespread and with a broken pattern on the forearms and legs – so-called livedo racemosa – may be a powerful clue to a diagnosis of antiphospholipid syndrome or systemic vasculitis such as polyarteritis nodosa. Examination of the hands will also show the extent of any damage from rheumatoid arthritis, and nodule formation may be seen over the fingers or at the elbows. The finding of periungual erythema with macroscopic nailfold capillary loops, Raynauds' phenomenon, and sclerodactyly with digital ulcers is pathognomonic for systemic sclerosis. Similarly, in a patient with respiratory failure, the presence of Gottron's sign and a heliotrope rash may indicate severe respiratory muscle weakness due to an inflammatory myopathy such as dermatomyositis.

Careful examination of the scalp may reveal discoid lesions with scarring alopecia of lupus. Examining the ears for skin lesions such as discoid lupus, cutaneous vasculitis, and fluid levels/tympanic membrane perforations may yield useful diagnostic information. Large nasal polyps in the context of late-onset asthma may point toward a diagnosis of Churg–Strauss syndrome. Schirmer's test for dry eyes is easily performed at the bedside and can be surprisingly helpful where an autoimmune connective tissue disorder is part of the differential diagnosis.

Cardiovascular examination for cardiac murmurs, signs of cardiac failure, absent or diminished peripheral pulses, and vascular bruits including listening for abdominal bruits may be helpful. Respiratory examination may reveal crepitations, signs of consolidation, or pleurisy. Stridor may indicate subglottic stenosis in Wegener's granulomatosis or tracheal collapse in relapsing polychondritis. However, clinical examination can be misleading. For example, patients with acute flares of Wegener's granulomatosis may have multiple cavitating pulmonary nodules that are not detected by simple bedside clinical methods. Likewise, patients with pulmonary hemorrhage often do not have obvious hemoptysis and there may be few if any detectable clinical signs in the lung fields.

Abdominal examination including rectal examination when appropriate in a patient with acute intestinal or mesenteric vasculitis may reveal signs of an acute abdomen or gastrointestinal hemorrhage due to bowel perforation or organ infarction. A careful neurological examination for motor or sensory deficits, which can be subtle, is essential.

A pattern of nerve damage suggesting mononeuritis multiplex or cranial neuropathies is a strong pointer to a vasculitic disorder. Likewise, lower limb long tract signs with bladder or bowel dysfunction may indicate transverse myelopathy in a patient with systemic lupus erythematosus. Fundoscopy should be performed wherever possible even in the absence of visual symptoms for signs of retinal vasculitis or hypertensive retinopathy as seen in patients with scleroderma renal crisis or a rapidly progressive glomerulonephritis.

In the locomotor system, the presence of an inflammatory arthropathy should be documented and the pattern of the arthritis can be useful diagnostically – there are only a few causes of a symmetrical inflammatory arthropathy: rheumatoid arthritis, systemic lupus erythematosus, and less commonly psoriatic arthritis. A monoarthritis in the context of a febrile patient should always be aspirated to investigate possible joint sepsis. A patient with acute urinary retention, bowel dysfunction, saddle anesthesia, and acute low back pain suggesting a large lumbar disk protrusion is a neurosurgical emergency.

This list is not exhaustive and the examination will be guided to large extent by the history and the patient's diagnosis if this is already known. It is therefore important for the clinician to have a thorough knowledge of the acute presenting features of the major multisystem rheumatic disorders and these will be described in detail in subsequent chapters of this book.

1.3.1 Investigations

At this stage, a diagnosis or a short differential diagnosis is usually possible allowing the clinician to discuss urgent investigations with colleagues. Simple investigations such as a full blood count, biochemistry, acute phase markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and a urine dip test for blood, protein, glucose, and leucocytes and a peak flow or simple spirometry at the bedside will provide useful information rapidly. In patients with autoimmune disorders such as lupus, a low CRP is very helpful as it lessens the likelihood of major bacterial infection. Likewise, a pancytopenia in a patient with previously normal blood counts could suggest either a lupus flare or bone marrow suppression from a cytotoxic drug. The presence of proteinuria and hematuria in the context of impaired renal function should lead to a search for dysmorphic red cells and granular casts in patients with systemic rheumatic diseases such as lupus or vasculitis where glomerulonephritis can lead rapidly to renal failure.

In patients with extensive skin manifestations, the differential diagnosis between a drug reaction and a cutaneous flare of lupus or systemic vasculitis can be difficult and a dermatology opinion and a skin biopsy may be helpful.

Imaging investigations need to be carefully selected to maximize clinical information gathering, balancing the risks of the investigation carefully. For example, in a patient with severe neurological manifestations, magnetic resonance imaging can yield critical information but this has to be set against the risk of contrast reactions and the possibility of nephrogenic dermal fibrosis due to gadolinium in patients with renal failure. Likewise, intra-arterial angiography in a patient with lupus, accelerated atherosclerosis, and gangrene may be combined with angioplasty or stent placement, but these procedures should

be undertaken in centers with vascular surgery support. New-generation spiral computed tomography scanners now offer the ability to rapidly acquire good quality vascular imaging to identify arterial bleeding or thrombosis relatively noninvasively and may in time replace conventional arteriography as the initial investigation of choice.[3]

1.3.2 Treatment Approaches

The most important urgent treatments are those outlined above to rapidly stabilize the patient and allow transfer either directly to the critical care unit or to a larger center with expertise in the management of complex rheumatological patients. The diagnosis of the immediate clinical problem and the underlying rheumatological diagnosis will dictate the treatment approach. The specific management of the individual disease and treatment complications will be covered in later chapters, but before commencing treatment, it is worth considering the following points:

- A number of diseases can mimic the autoimmune rheumatic disorders. Good examples include infections such as subacute bacterial endocarditis (SBE) mimicking vasculitis, especially as low titer autoantibodies commonly occur in SBE. Other mimics include malignancy, atrial myxomas, and viral infections such as HIV which can mimic both lupus and Sjogren's syndrome.
- There should never be a rush to commence immunosuppressive agents until a thorough evaluation for infection has been performed. If the patient is overtly septic and has a rapidly progressive autoimmune rheumatic disorder such as lupus or systemic vasculitis, intravenous immunoglobulin, if available, can be useful as a short-term measure.
- Patients should be assessed frequently on the critical care unit for the development of unexpected complications including adverse effects from therapy and new organ disease manifestations of the underlying disorder.
- Failure to respond to a treatment protocol should lead to a reevaluation of the diagnosis.

1.3.3 Complications from Prolonged Immobilization

Patients with rheumatic disorders are even more likely than usual to develop complications from prolonged in-patient admissions and immobility. Attention should be paid to the risk of muscle wasting and joint contractures with early assessments and interventions from a physiotherapist and occupational therapist. Patients may be at risk of critical care neuropathies and these should be distinguished from the neuropathies that may occur for example in rheumatoid arthritis, lupus, or the vasculitides. Decubitus ulcer is a particular problem in patients who have been on long-term corticosteroid therapy where the skin has become thin and friable – intensive nursing care is essential in the prevention of these difficult-to-treat ulcers. Immobility will also exacerbate the risk of osteoporosis in these patients, and specific therapies such as calcium and vitamin D supplementation and bisphosphonates

should be considered. Nutrition can be a problem in patients with systemic sclerosis who have dysphagia or malabsorption due to bowel involvement. Autoimmune rheumatic patients are at increased risk of venous thromboembolism, and the presence of antiphospholipid antibodies together with traditional cardiovascular risk factors will exacerbate this risk. It is vital therefore that these patients should be assessed for the risk of thrombosis on admission and managed accordingly.

1.3.4 End-of-Life Decisions

Critical care units are faced with decisions about withdrawal of active interventions on a daily basis. While patients with rheumatic disorders are usually young women of childbearing age, many patients with systemic vasculitis and rheumatoid arthritis are older with multiple comorbidities. The decision to withdraw active treatment from a young patient with little or no hope of recovery from advanced scleroderma, for example, can be difficult. However, guidelines and specific training programs exist for open discussion of these issues with patients and their carers in a sensitive manner and to ensure that a high standard of care continues to be delivered in the last days and hours of the patient's life.

1.4 Conclusion

In summary, patients with autoimmune rheumatic disorders often present acutely and may need admission to a critical care unit. The outcome of these patients is still poor but will be significantly enhanced if clinicians have a good working knowledge of the often nonspecific presentations of these patients together with the ability to rapidly assess patients and liaise with colleagues in formulating a management plan and determining the ideal environment in which to deliver critical care.

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Life-Threatening Complications of Systemic Lupus Erythematosus

2

Michelle Petri

Abstract The major cause of death in longstanding lupus is accelerated atherosclerosis leading to cardiovascular disease. Early in lupus, the major causes of death are active lupus and infection. Life-threatening or organ-threatening lupus is not rare. Multiple organs including skin (necrosis), hematologic (thrombocytopenia, hemolytic anemia, neutropenia, catastrophic antiphospholipid syndrome, and thrombotic thrombocytopenic purpura), heart (pericardial tamponade, myocarditis), lung (alveolar hemorrhage, pulmonary hypertension), gastrointestinal (vasculitis, pancreatitis), adrenal insufficiency, and neurologic (myelitis) may be encountered.

Keywords Catastrophic antiphospholipid syndrome • Hemolytic anemia • Myelitis • Myocarditis • Pancreatitis • SLE • Thrombocytopenia • Vasculitis

2.1 Introduction

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease. It has a strong female predominance (9:1) and predominantly is diagnosed in the 20's and 30's. SLE and its treatment lead to important morbidity and mortality. Because SLE is a multisystem disease, the following chapter will divide emergencies by organ system. For each emergency, the manifestation will be described, its evaluation detailed, and initial treatment discussed.

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2.2 Cutaneous Digital Gangrene

Digital gangrene in SLE may start as small ischemic lesions but can quickly progress to digital gangrene. In the largest series, long disease duration, Raynaud's phenomenon, and elevated serum CRP were independent risk factors.[1] The differential diagnosis includes severe Raynaud's phenomenon, thromboembolic (i.e., antiphospholipid syndrome [APS]), and lupus vasculitis. Evaluation requires the assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-beta$_2$-glycoprotein I), cardiac echocardiogram, and often arteriogram.

Treatment of digital gangrene is multifactorial. If vasospasm (Raynaud's) is involved, calcium channel blockers will be given. Other vasodilators, including topical nitrates, may be tried, as well. Intravenous prostacyclin may be needed. To prevent and treat thrombosis, low-dose aspirin (81 mg) and therapeutic doses of heparin are needed. If lupus vasculitis is present, intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min), followed by high-dose oral prednisone (1 mg/kg) is started. Digital sympathectomy, if an experienced surgeon is available, may be considered. The goal is to save as much ischemic tissue as possible. Once tissue demarcation has occurred, a hand or vascular surgeon may amputate the gangrenous areas to relieve pain and improve cosmetic appearance.

2.3 Cutaneous Necrosis

Widespread cutaneous necrosis is rare in SLE. It can occur from antiphospholipid syndrome,[2] SLE vasculitis, and can be induced by warfarin in patients who are Protein C deficient (because warfarin further reduces Protein C and Protein S levels). Evaluation will include assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-beta$_2$-glycoprotein I) and biopsy of the edge of a necrotic area (to detect vasculitis). If the necrosis is due to APS, therapeutic doses of heparin are started. If necrosis is due to SLE vasculitis, IV methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) is given, followed by high-dose oral prednisone (1 mg/kg).

2.4 Thrombocytopenia

Thrombocytopenia is common in SLE and is one of the American College of Rheumatology classification criteria for SLE.[3] In the Hopkins Lupus Cohort, 21% have had thrombocytopenia defined as a platelet count less than 100,000/mm^3. Most thrombocytopenia in SLE

is not life-threatening, and, in fact, may be over-treated. It is rare for patients to bleed unless the platelet count is below 10,000; treatment usually is not needed unless the platelet count falls below 30,000/mm^3. An exception is made in an anti-coagulated patient, in whom the goal is to keep the platelet count above 50,000/mm^3. Evaluation of thrombocytopenia in an SLE patient includes assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-beta$_2$-glycoprotein I), antiplatelet antibodies, drug toxicity, and infection. Rituximab can cause a very rare thrombocytopenia, with recovery usually within 2 weeks.

Treatment of serious thrombocytopenia requires intravenous methylprednisolone (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg). Some patients, however, may not respond. Intravenous immunoglobulin, 400 mg/kg over 5 days, is usually the next step; it may be necessary to increase the dose to 1 kg/kg to see a response. In those who still do not respond, rituximab can be considered. Maintenance therapy with azathioprine or mycophenolate is usually needed. Platelet transfusions can be given to patients who are actually bleeding, but the SLE patient's autoantibodies will rapidly destroy them. A patient who responds to intravenous immunoglobulin, but frequently relapses, is a candidate for splenectomy. Although it should not be considered a cure, most patients do improve postsplenectomy. A patient who is not a surgical candidate can be considered for splenectomy by radiation. Newer agents for thrombocytopenia, such as Promacta® (eltrombopag), have not been adequately assessed in SLE, and would not be routine in an emergent situation.

2.5 Autoimmune Hemolytic Anemia (AIHA)

AIHA is rare in SLE, occurring in only 11% of the Hopkins Lupus Cohort. Evaluation for AIHA would include a search for other causes of anemia (ferritin, B12, hemoglobinopathy, schistocytes) as well as tests to confirm hemolytic anemia (direct Coombs test, low haptoglobin, high LDH, high reticulocyte count).

Treatment of AIHA includes intravenous methylprednisolone (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg). Maintenance therapy with azathioprine or mycophenolate mofetil[4] is then given. Danazol has been used.[5] Refractory AIHA may require rituximab[6,7] or splenectomy.[8]

2.6 Neutropenia

Leukopenia in SLE is common and is part of the American College of Rheumatology classification criteria. Most leukopenia in SLE is lymphopenia; neutropenia from SLE is rare, but reported.[9,10] Evaluation of neutropenia in SLE would include anti-neutrophil antibodies

and drug toxicity (usually cyclophosphamide or other immunosuppressive drugs). Rituximab can cause both an immediate and a late neutropenia.

Neutropenia in SLE is usually not an emergency; it is often over-treated. As long as the total neutrophil count is above 1,000/mm^3, the risk of infection is small, and no treatment is necessary. If the patient becomes neutropenic due to cyclophosphamide, or other immunosuppressive drug, it is sufficient to stop the cyclophosphamide and allow the neutrophils to recover. Granulocyte colony stimulating factor (G-CSF) should not be given to the stable patient because of the risk of SLE flares (including fatal flares).[11] G-CSF should be reserved for the neutropenic patient with sepsis.

2.7 Catastrophic Antiphospholipid Syndrome (CAPS)

CAPS is a rare manifestation of APS. About 40% of CAPS patients have SLE; 10% another rheumatic disease; and 50% no history of autoimmune disease. Common precipitants include infection, surgery, trauma, pregnancy, oral contraceptives, and cessation of warfarin in an APS patient. "Definitive" CAPS requires three organ involvement, and demonstration of thrombosis in the setting of antiphospholipid antibodies. "Probable" CAPS requires involvement of two organs. CAPS manifestations differ from APS. In CAPS, 48% have primary APS, 40% have SLE, and 12% have secondary APS due to another cause.[12] Evaluation of CAPS involves assessment of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-$beta_2$-glycoprotein I), examination of the peripheral smear for microangiopathic hemolytic anemia and documentation of thrombosis.[13]

Treatment is truly an emergency, as mortality is as high as 50%. Treatment has three goals: to settle the "cytokine storm" (intravenous methylprednisolone pulse), treat and prevent further thrombosis (intravenous heparin), and reduce the antiphospholipid antibody burden (plasmapheresis or intravenous immunoglobulin).[13] In recalcitrant cases, rituximab may be helpful.

2.8 Thrombotic Thrombocytopenic Purpera (TTP)

Past series of TTP in SLE may have included some patients with CAPS, as the two can present in similar fashion.[14,15] Genetic or autoantibody-induced deficiency of the metalloproteinase ADAMTS13 is part of the pathogenesis. Classic TTP includes fever, thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, and neurologic involvement.[16] Evaluation would include a peripheral blood smear for schistocytes, exclusion of infection, and drug toxicity.

Treatment of TTP in SLE is plasmapheresis or plasma exchange.[17] Intravenous cyclophosphamide and rituximab have also been used.[18,19]

2.9 Pericardial Tamponade

Pericarditis is frequent in SLE, occurring in 22% of the Hopkins Lupus Cohort. Serositis is one of the ACR classification criteria of SLE. Pericardial tamponade, however, is rare. It can occur as a presenting manifestation of SLE.[20] Typically, pericarditis is positional, such that the patient feels dyspneic lying flat and feels better leaning forward. Patients with tamponade may present with ascites and edema.[21] Evaluation would include physical examination findings including pericardial rub, distant heart sounds, pulsus paridoxus, and confirmatory cardiac echocardiogram.

Treatment of life-threatening pericardial tamponade will require a pericardial tap or pericardial window. Treatment of the underlying SLE activity would include intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg).

2.10 Myocarditis

SLE myocarditis is rare, occurring in 14% in one series.[22] It may be associated with myositis.[23] Patients with SLE myocarditis often present with congestive heart failure. Evaluation would include cardiac echocardiogram, which would show hypokinesis, and coronary arteriogram to rule out atherosclerosis or coronary vasculitis. On occasion, a right ventricular biopsy confirms myocarditis.[24]

Treatment of myocarditis would include intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg).[25] Pulse cyclophosphamide therapy may be needed.[26]

2.11 Pulmonary Alveolar Hemorrhage

Alveolar hemorrhage is extremely rare in SLE, with only a few case series.[27-29] It presents as dyspnea, fever, hemophysis, and chest pain. Evaluation would include chest CT and bronchoscopy.

Treatment of alveolar hemorrhage in SLE is plasmapheresis and intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg).

2.12 Pulmonary Hypertension

Pulmonary hypertension in SLE can be severe, with a poor prognosis.[30] Dyspnea is the most common presenting symptom. Evaluation of an SLE patient with acute severe pulmonary hypertension would require cardiac echocardiogram followed by right heart catheterization. The immediate concern is whether it is due to thromboembolic disease or due to SLE activity.

Treatment of pulmonary hypertension due to thromboembolic disease may require surgical embolectomy or thrombolytic agent or heparin. Severe pulmonary hypertension due to active SLE is treated with intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min) followed by high-dose oral prednisone (1 mg/kg). Chronic pulmonary hypertension can be treated in a fashion similar to idiopathic pulmonary hypertension, including sildenafil, bosentan, and intravenous prostacyclin.[31]

2.13 Pancreatitis

Pancreatitis is a rare manifestation of SLE. In the largest review, only 4% of SLE patients had pancreatitis attributed to SLE.[32] Patients present with abdominal pain, fever, and electrolyte disturbances. It can be fatal, especially in pediatric patients.[33] A multivariate model found that hypertriglyceridemia, psychosis, pleurisy, gastritis, and anemia were associated with a history of pancreatitis.[32] Although antiphospholipid antibodies can occur, they do not appear to be causative.

Although high-dose corticosteroids can cause pancreatitis, when SLE pancreatitis occurs, intravenous methylprednisolone 1,000 mg daily for 3 days remains the treatment of choice.

2.14 Adrenal Insufficiency

Adrenal insufficiency is a very rare manifestation of SLE. It appears in conjunction with antiphospholipid syndrome, or more commonly, in catastrophic antiphospholipid syndrome (CAPS), in whom 26% had adrenal involvement in one series.[12,34] In CAPS, adrenal involvement is usually bilateral, due to adrenal venous infarction. Adrenal insufficiency usually presents acutely, with flank pain, nausea, vomiting, hypotension, and electrolyte abnormalities.

Treatment of CAPS is reviewed elsewhere in this chapter. Management of adrenal insufficiency is both acute, in terms of steroid, volume and electrolyte management, and chronic, with adrenal replacement, with low-dose prednisone and fluorinated steroids.

2.15 Mesenteric Vasculitis

Mesenteric vasculitis is a very rare manifestation of SLE. Patients present with fever, abdominal pain, diarrhea, vomiting, and sepsis.[35,36] Early in the course, swollen layers of bowel may be present on abdominal CT.[37] A mesenteric arteriogram may show vasculitis. Occasionally, biopsy during colonoscopy may reveal vasculitis. The differential diagnosis would include atherosclerosis, pancreatitis, peptic ulcer, peritonitis, bowel infarction, and infection (such as *C. difficile* or cytomegalovirus).

Management requires both surgical resection of dead bowel and suppression of vasculitis by intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min).

2.16 Myelitis

Longitudinal myelitis in SLE occurs in two forms, one affecting gray matter (that occurs in an acute catastrophic form) and one involving white matter (that clearly resembles neuromyelitis optica).[38] Myelitis presents as pain, weakness, and sphincteric defects. Patients with gray matter involvement will have flaccidity and hyporeflexia, while patients with white matter dysfunction will have spasticity and hyperreflexia. Patients with gray matter dysfunction may have a prodrome of fever and urinary retention. Those with white matter involvement are more likely to have had antiphospholipid antibodies.

Treatment for SLE myelitis needs to be given within a short time after symptom onset, with intravenous methylprednisolone pulse therapy (1,000 mg daily for 3 days, given over 90 min), followed by high-dose oral corticosteroids. There may be a role for rituximab, as well.

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