Rheumatological emergencies – Perspective of an intensivist.

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ABSTRACT

Rheumatological disorders include a diverse range of disorders characterized by chronic inflammation and autoimmunity. Rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis are some common conditions that present to the intensive care unit (ICU). Emergencies due to these rheumatological disorders can present in different forms. Multiple organ system involvement in critically ill patients may be due to various conditions which creates a diagnostic dilemma. Prompt identification and management of devastating complications of the disease itself or associated therapeutics are of great challenges for critical care physicians. Early detection of disease-specific complications, and patient-tailored therapeutic interventions are crucial for optimal patient outcomes. Collaboration between rheumatologists, intensivists, and other relevant professionals is paramount in the management of rheumatological emergencies in ICU. This review focuses on common rheumatological emergencies that are encountered in ICU.

Keywords: emergencies, ICU, rheumatologic.

INTRODUCTION

Autoimmune rheumatologic diseases are multisystem disorders with a plethora of manifestations. These are usually chronic in nature and manifestations evolve over a period of time. However, acute and life-threatening events are not that uncommon. Approximately 10-25% of patients with rheumatologic disease presenting to the emergency department require hospitalization. More than 50% of hospitalizations are due to infections, and 25% to 35% are due to worsening rheumatic diseases. One-third of these require intensive care.[1] Rheumatoid diseases that frequently require ICU admission are systemic lupus erythematosus (SLE), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, rheumatoid arthritis, scleroderma, and dermatomyositis. Most common rheumatological causes for ICU admission are development of new manifestations or end organ sequelae of rheumatological disorders, infection secondary to immunosuppressive treatment, adverse effects of disease-modifying drugs or even acute critical compromise unrelated to but exacerbated by the underlying disorders. Patients can present to ICU with diverse clinical manifestations with multiorgan involvement.[2,3]

Patients with different rheumatological disorders can present in an ICU with diverse clinical manifestations (Table. 1). One of the prime challenges lies in the timely differentiation of these disorders from other diagnoses with multiorgan involvement such as sepsis. Insight from an experienced rheumatologist may be required in some circumstances. Mortality from rheumatological emergencies is variable and has been reported up to 20% in some of the studies.[4] In this review, we aim to elaborate some of the systemic emergencies in patients with underlying rheumatological conditions that often create dilemmas among ICU physicians.

Table 1. Common clinical manifestations of different rheumatological disorders

Organ system involved	Clinical manifestation	Common rheumatic conditions
Nervous system	Seizure Meningitis Delirium Psychosis Infarction Hemorrhage PRES Dural sinus thrombosis Acute visual loss Mononeuritis multiplex	SLE Scleroderma Antiphospholipid syndrome Drugs-NSAIDS Vasculitis Scleroderma Antiphospholipid syndrome Drugs-NSAIDS Vasculitis
Cardiovascular system	Coronary artery syndrome Arrhythmias Heart blocks Cardiac tamponade Hypertensive emergencies Aortic dissection Myocarditis Endocarditis	Rheumatoid arthritis Large, medium and small vessel vasculitis Scleroderma SLE Antiphospholipid antibody syndrome
Respiratory system	Pneumonia Pulmonary alveolar hemorrhage Pleural effusion Pulmonary hypertension Airway involvement (Subglottic stenosis)	SLE Dermatomyositis Goodpasteur's syndrome Rheumatoid arthritis Granulomatosis with polyangiitis Relapsing polychondritis

Gastrointestinal system	Gastrointestinal bleeding Gut Infarction Mesenteric Ischemia Pancreatitis Hepatic failure	SLE IgA vasculitis Still's disease Drugs Granulomatosis with polyangiitis Scleroderma
Renal System	Rapidly progressive renal failure Renovascular hypertension Spontaneous perinephric hemorrhage Scleroderma renal crisis Perinephric	SLE GPA/MPA PAN Scleroderma
Endocrine system	Hypothyroidism Hypoglycemia Adrenal insufficiency	Scleroderma Exogenous Cushing Acute stress, Sudden omission Drugs-Hydrochlorothiazide
Hematological system	Anemia Leucopenia Thrombocytopenia Coagulopathy Pancytopenia Macrophage activation	SLE Adult onset Stills disease Antiphospholipid syndrome Systemic onset JIA DMARDs toxicity

Pulmonary-Renal Syndrome (PRS)

This is a life-threatening condition characterized by renal failure along with respiratory distress. PRS manifests in the form of rapidly progressive glomerulonephritis with diffuse alveolar hemorrhage (DAH).[5] This was described for the first time by Goodpasture in 1919 AD. 70-90% cases are accounted for by anti-Glomerular basement disease (anti GBM) and anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. Other ANCA negative vasculitis like SLE, antiphospholipid syndrome, thrombotic thrombocytopenic purpura, drug induced diffuse alveolar hemorrhage, IgA vasculitis may infrequently present with PRS.[6,7]

Pathogenesis

In most of the cases, small vessel vasculitis affects the alveoli and glomeruli. Neutrophilic infiltration of the vascular endothelium leads to inflammatory response affecting the arterioles, venules and capillaries. This leads to the destruction of vessel wall and necrosis, which may be granulomatous or fibrinoid.[8] In alveoli, beside these, necrotizing pulmonary capillaritis can be noted. The interstitium gets filled with neutrophils, oedema and fibrin thrombi eventually causing fibrinoid necrosis. The integrity of interstitial capillaries becomes damaged during this process, allowing red blood cells to cross the now incompetent alveolar capillary basement membranes, entering the interstitial space and flooding the alveoli.[9]

Clinical presentation

The classical manifestation includes hemoptysis, hypoxemia, drop in hemoglobin, and diffuse alveolar infiltrate. However, nonspecific presentation usually creates diagnostic dilemmas during the early phase.

Diffuse alveolar hemorrhage and glomerulonephritis are the usual unifying features. DAH presents with hemoptysis, but may be absent in 30% cases. Hemoptysis is usually mild. Other manifestations include cough and fever, often progressing to respiratory failure requiring support. Hematuria, proteinuria and urinary sediments are other usual presentations of glomerulonephritis. This may progress to end stage renal disease requiring renal replacement therapies. Chest X-ray may be normal in one fourth of cases. Ground glass opacities, alveolar infiltrates and consolidations are the usual CT findings (Fig 1 and 2). These findings may resolve after 3-4 days of cessation of hemorrhage.[10,11]
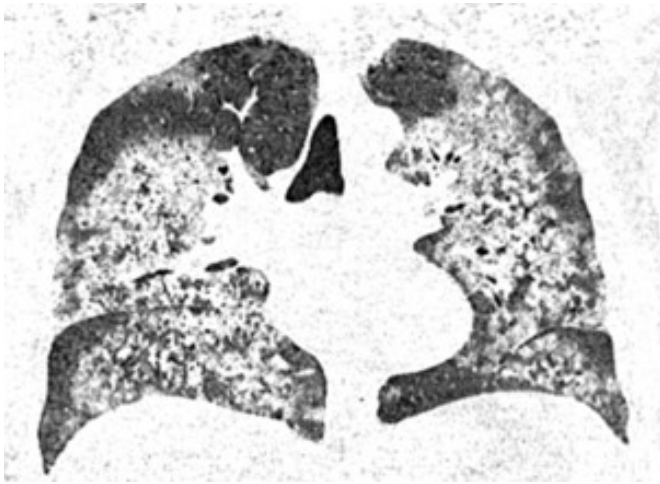
Figure 1. CT scan of lung, coronal view, showing bilateral diffuse perihilar opacities in a patient with Diffuse Alveolar Hemorrhage.
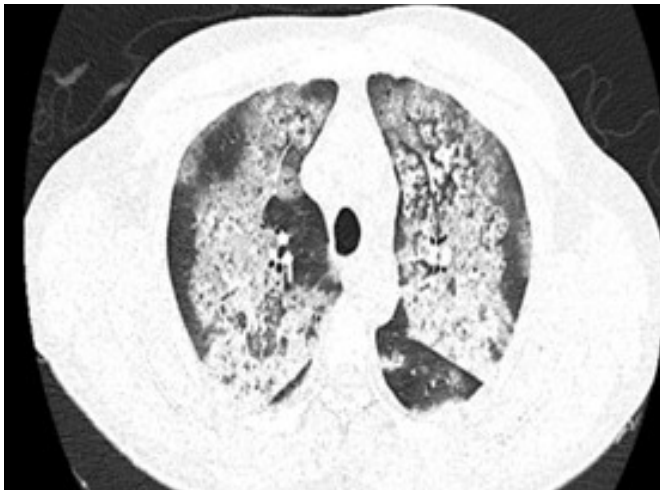

Figure 2. CT scan of lung, axial view, showing bilateral diffuse perihilar opacities in a patient with Diffuse Alveolar Hemorrhage.

Diagnosis

Bronchoalveolar lavage is required to confirm DAH in which repeated samples will show increasing blood tinge and cytology will reveal hemosiderin-laden macrophages. Laboratory findings include normocytic normochromic anemia and presence of proteinuria, dysmorphic RBC, RBC casts on urine analysis. Serological testing to detect anti-GBM antibodies can be done. The gold standard, however, is renal and lung biopsy.[11,12]

Management

Management represents a major challenge as mortality is of the order of 25–50%. Mainstay of ANCA associated PRS and Good pasture's syndrome is immunosuppression. 3-5 days of high dose steroid with or without cyclophosphamide are used for remission. Once remission is achieved, steroid is then continued at a tapering dose for around 3-5 months with cyclophosphamide continued for 6-12 months. Plasmapheresis is thought to be helpful during acute settings. Plasmapheresis is likely to dilute down ANCA titers and

removes a large fraction of pro-inflammatory cytokines, complement and coagulation factors from the systemic circulation. However, the role of plasmapheresis has been a matter of debate after the result of PEXIVAS trial was out. Treatment with plasmapheresis was not associated with reduced incidence of death or end stage renal disease. Serum creatinine and age at presentation are independent predictors of poor prognosis.[11-14]

Sclerodermal renal crisis

It is a life-threatening complication of Systemic Sclerosis (scleroderma) characterized by sudden onset severe hypertension, hypertensive encephalopathy and rapidly progressive renal failure. Prevalence is around 10-25% in diffuse compared to 1-2% with limited disease. 75% of the cases occur within 4 years of disease.[15] Risk factors for SRC include diffuse skin involvement, glucocorticoid use, serum autoantibodies, use of cyclosporine, new onset anemia, new cardiac events like heart failure .[16-18]

Pathogenesis

Pathogenesis of sclerodermal renal crisis is not fully understood. It is believed that the damage to the endothelial cells causes early structural alterations in the blood arteries (intimal thickening and proliferation, fibrin deposition). This leads to renal ischemia, hyperplasia of the juxtaglomerular apparatus, activation of the renin-angiotensin-aldosterone system (RAAS), and rise in blood pressure. All these changes are brought upon by decreased renal blood flow caused by structural changes in the blood vessels as well as renal vasospasm (Raynaud's phenomenon). Blood vessel damage is exacerbated by the rise in blood pressure, creating a vicious cycle that eventually results in malignant hypertension.[19,20]

Clinical presentation

Acute renal failure (oligo-anuric) and abrupt onset hypertension are the common presentations. Other manifestations include non-nephrotic proteinuria, hematuria, hypertensive encephalopathy with headache, disorientation, and visual abnormalities.[19,20]

Diagnosis

Anemia and thrombocytopenia may be discovered via laboratory testing. Most cases are clinically diagnosed; however, kidney biopsies may be necessary. Common disorders that resemble sclerodermal renal crisis include thrombotic microangiopathy, malignant hypertension, and rapidly progressing glomerulonephritis.[20-22]

Management

Patient needs to be hospitalized after diagnosis. The main goal of treatment is to manage blood pressure effectively and quickly. ACE inhibitors are the necessary component of the therapy for the blockage of the RAAS crucial to the pathogenesis of this condition. The treatment is usually started with short-acting medications, such as captopril, and

dosage increased rapidly to reduce systolic blood pressure (BP) by roughly 20 mm Hg in 24 hours, achieving the target BP of 120/70 mm Hg in 72 hours, all the while avoiding hypotension. Once the desired blood pressure has been reached and the dose has stabilized, long-acting ACEI can be substituted in equal amounts. If the BP is still not under control, dihydropyridine calcium channel blocker should be administered. Renal function may continue to decrease, but therapy should be continued because about 50% of these patients may make enough of a recovery over 3 to 18 months. Patients on ACE inhibitors can currently expect an 85% survival rate after one year and a 65% survival rate after five years. Diuretics however, should be avoided as they can exacerbate the clinical state by activating RASS even more. Since endothelin-1 levels have been observed to be elevated in these situations, endothelin receptor antagonists may play a part.[21,22] Other treatments include kidney transplantation and dialysis. Successful kidney transplantation dramatically increases odds of survival as compared to long-term dialysis, and it is extremely rare (less than 5%) for SRC to recur in transplanted kidneys.[23]

Macrophage activation syndrome (MAS)

This is a rare but life-threatening presentation of various rheumatological disorders. MAS is often grouped under the umbrella of Hemophagocytic Lymphohistiocytosis (HLH) and is associated with a mortality rate between 15-20%. MAS was first described in 1985 by Ramanan and Schneider as a syndrome of "HLH with underlying rheumatological disease." Since then, the diagnostic criteria for MAS have been refined and the syndrome is now recognized as a distinct entity from HLH.2[4] Primary HLH is caused by genetic defects in perforin genes and presents mainly in infants. Secondary, acquired forms of MAS/HLH occur in malignant disease, those with acquired immune deficiency states, such as organ transplant recipients, and in those with RD. MAS/HLH is often associated with systemic juvenile idiopathic arthritis, SLE, adult onset Still disease or those with immune deficiency as with organ transplant. MAS can also develop in ICU patients suspected to have sepsis with multiorgan dysfunction without any rheumatological conditions. Usually trigger for such cases are EBV infections and Lymphoma.[25]

Clinical features

Underlying hyperinflammatory state results in most of the clinical presentation. Most common presenting features are fever, hepatomegaly, and splenomegaly. Bicytopenia often thrombocytopenia, hyperferritinemia, coagulopathy/disseminated intravascular coagulation, lymphadenopathy, hypertriglyceridemia, neurological features such as confusion, seizure, coma, multiorgan failure are other important features.[26,27]

Diagnosis

The diagnosis of MAS can be challenging, as it requires a high index of suspicion and a combination of clinical, laboratory, and histological findings. The diagnostic criteria for MAS include fever, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, elevated ferritin, and evidence of macrophage activation (such as hemophagocytosis in bone marrow biopsy or elevated soluble interleukin-2 receptor levels).[27,28]

Management

Early recognition and prompt treatment are key to improving outcomes in patients with MAS. Treatment of MAS includes a combination of immunosuppressive and supportive therapies. High-dose corticosteroids are the first line of treatment, but other immunosuppressants, such as cyclosporine, cyclophosphamide, and intravenous immunoglobulin, can be used in refractory cases. Supportive measures, such as removal of the triggering agent, infection control, blood product transfusion and mechanical ventilation, may also be needed in severe cases.[29]

Catastrophic antiphospholipid syndrome (CAPS)

Catastrophic antiphospholipid syndrome is the most severe presentation of antiphospholipid syndrome (APS). It is characterized by severe thrombotic complications, usually microvascular as well as large vessel thrombosis, affecting multiple organs. The most commonly affected organ systems include the kidney, lung, central nervous system, heart, and skin. Approximately 1% of patients with APS develop the severe clinical picture of CAPS. Infection is the most common trigger for CAPS in around half of cases. Other common precipitating factors include trauma, surgery, pregnancy, withdrawal of anticoagulants.[30,31]

Pathogenesis

It involves multiple organs simultaneously with a diffuse, micro or combined micro and macrovascular process. Activation of immune cells and coagulation factors with release of neutrophil extracellular traps, complement activation all are attributed for pathological process. There is also production of antiphospholipid antibodies, which can lead to an increased risk of blood clots.[32]

Clinical features

Clinical manifestations of CAPS are related to two factors: the extent of thrombosis and organs directly affected by them and manifestations of the SIRS promoted by cytokine storm. Renal involvement occurs in 74% and often present with fever, hypertension, hematuria. ARDS, pulmonary embolism and pulmonary hemorrhage are the manifestation of pulmonary involvement. With CNS involvement, patients may present with seizure, confusion, encephalopathy and/or focal deficits. Abdominal pain may reflect intra-abdominal thrombotic complications. Purpura, sublingual hemorrhage, skin necrosis, myocardial infarction are some other manifestations. Laboratory evaluation reveals thrombocytopenia, evidence of hemolysis and features of disseminated intravascular coagulation.[32,33]

Diagnosis

Well validated diagnostic criteria are not available. High level of suspicion for CAPS should be maintained in any patient with features of multiorgan involvement, rapid clinical deterioration within a week and findings of hemolytic anemia. Besides these, histological confirmation of small vessel occlusion and presence of anti-phospholipid antibodies favors the diagnosis of CAPS.[34,35]

Management

CAPS is usually treated with a combination of anticoagulation, glucocorticoids, and therapeutic plasma exchange (TPE) or intravenous immune globulin (IVIG), sometimes referred to as triple therapy. Anticoagulation prevents as well as treats the thrombotic complication whereas steroids counteract the cytokine storm. Intravenous cyclophosphamide is recommended in patients when CAPS is associated to SLE.[36,37]

Small case series have generated evidence for use of rituximab or eculizumab in cases which are refractory to triple therapy. Beside these treatments, any condition that triggered CAPS needs to be treated.[38,39] Despite aggressive treatment, mortality is very high exceeding 30% and mostly due to infections, cerebrovascular events and cardiopulmonary failure.[40]

CONCLUSION

Autoimmune rheumatological diseases can present in different forms and affect all organ systems. A high index of suspicion and appropriate testing in an appropriate clinical setting will aid in the timely diagnosis of these diseases. A multidisciplinary approach combined with current therapies (steroids, IVIG, plasmapheresis) can improve outcome when started early. New treatments such as rituximab are being studied and show promising results in some cases. Intensivists should be aware of these rare but life-threatening emergencies as these emergencies can be treated if they are identified early in the course of disease.

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