Chapter 246: Rheumatologic Emergencies

Derrick J. Todd; Paul F. Dellaripa

INTRODUCTION

Key Clinical Questions

1. What are the signs and symptoms of cervical spine involvement in rheumatoid arthritis and the spondyloarthritides?
2. What tests should be ordered in patients with suspected pulmonary-renal syndrome?
3. Which patients with interstitial lung disease are most likely to respond to corticosteroids?
4. What are common and uncommon clinical signs and symptoms associated with giant cell arteritis?
5. What factors portend an impending renal crisis in a patient with known scleroderma?
6. What are the risk factors for Raynaud digital crisis? What treatments reduce morbidity?

Rheumatologic diseases rarely present as an acute emergency. However, when they do, a delay in diagnosis can lead to significant morbidity and mortality. The most important and common examples of this include: (1) cervical spine involvement in inflammatory arthritides; (2) recognition of the protean presentations of giant cell arteritis so as to prevent permanent visual loss; (3) early diagnosis of pulmonary-renal syndromes which, if unrecognized, can lead to life-threatening respiratory failure and renal failure; and (4) scleroderma renal crisis, in which a delay in diagnosis can mean the missing of the therapeutic window in which renal function can be rescued. In each of these conditions, involvement of a rheumatologist is often warranted.

THE CERVICAL SPINE IN THE RHEUMATIC DISEASES

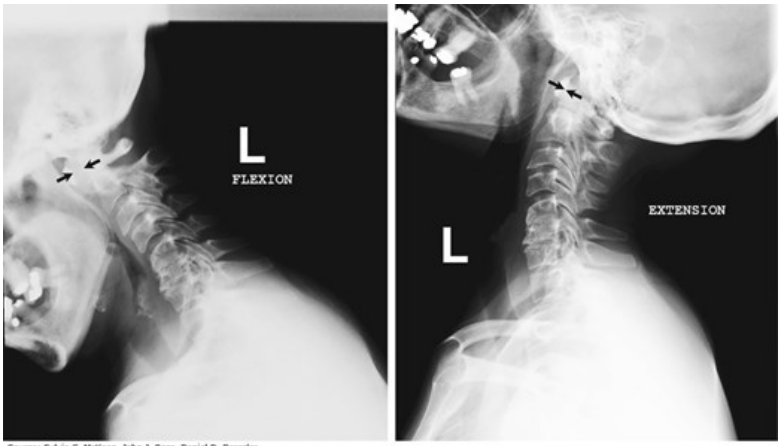
Catastrophic neurologic injury and even death may result from cervical spine disease in patients with rheumatoid arthritis (RA) or spondyloarthritis (SPA). Early recognition of the signs and symptoms and appropriate diagnostic evaluation are critical to avoid these complications.

ATLANTOAXIAL INSTABILITY

Up to 30% of patients with severe RA have some degree of subluxation of the atlantoaxial joint (C1-C2). In normal patients, the odontoid process of the axis (C2) is secured in front by the anterior arch of the atlas (C1), and posteriorly by the transverse ligament of the atlas. The normal distance between the odontoid process and the anterior arch of the atlas is 3 mm. Inflammation in the small joints that make up the atlantoaxial joint, or tenosynovitis of the transverse ligament of the axis, may weaken the transverse ligament, as well as lead to bony erosions in the odontoid process. As a result, the space between the odontoid and the anterior arch of the atlas widens (**Figure 246-1**), and the atlantoaxial joint becomes unstable. Anterior subluxation, in which the atlas slides forward relative to the axis, is the most common type of cervical spine emergency. It leads to cord compression and cervical myelopathy. Less commonly, posterior subluxation occurs when the odontoid is badly damaged or fractured. Rarely, vertical C1-C2 subluxation occurs, with atlanto-axial impaction, migration of the odontoid into the foramen magnum, brainstem compression, and death. Atlantoaxial instability may also produce vertebrobasilar insufficiency by impairing blood flow in the vertebral arteries, which travel through the transverse foramina of the cervical spine.

Figure 246-1

Cervical spine in rheumatoid arthritis, showing atlantoaxial subluxation. A lateral view of the upper cervical region shows posterior displacement of the odontoid process. In flexion view (left panel), preodontoid space measures approximately 5 mm (arrows). Normally this measurement should not exceed 2.5 to 3 mm in an adult, although in a child 4 to 5 mm may be within the normal range. The measurement is made at the mid-level of the anterior aspect of the dens with the neck held in flexion. Subluxation is not present on extension views (right panel). There is also severe disc space narrowing, sclerosis, and osteophyte formation at C5-C6 and C6-C7.



Symptoms of impending cervical spine subluxation may include occipital or retro-orbital headache, paresthesias of the extremities, and electric shock sensation in the upper extremities with neck flexion. Physical examination findings may include hyperreflexia, a positive Babinski test, and sensory loss in the hands and feet. Typically, patients with advanced cervical spine disease also demonstrate evidence of advanced disease elsewhere. Unfortunately, the neurologic examination in patients with advanced or aggressive RA or SPA may be confounded by muscle wasting, severe joint deformities, and entrapment neuropathies. Ominous symptoms and signs include a sensation of the head falling forward during neck flexion, syncope, respiratory irregularities, loss of sphincter control, dysphagia, hemiplegia, or nystagmus.

Lateral radiographs of the cervical spine in flexion and extension are the most useful initial diagnostic studies. These are diagnostic if the space between the anterior arch of the atlas and the odontoid is 9 mm or more, with an interval between the odontoid and the posterior arch of the atlas of less than 14 mm in the flexed position. In symptomatic patients, flexion and extension films should only be performed if standard films have excluded odontoid fracture and severe subluxation. When cervical spine radiographs are not diagnostic, magnetic resonance imaging (MRI) or computed tomography (CT) scan should be performed. MRI is particularly useful in delineating the extent of cord compression and the relationship of the odontoid to the brainstem, and in planning surgical stabilization. However, compared with flexion/extension radiographs, MRI may underestimate the degree of subluxation because patients remain supine for the study.

In the setting of progressive symptoms of cord compression, urgent neurosurgical consultation should be obtained for stabilization of the cervical spine. The role and timing of surgery in patients with atlantoaxial instability without cord compression is uncertain. The utility of medical therapy, such as rigid cervical collars and isometric neck strengthening exercises, is also unclear.

In patients with RA undergoing general anesthesia, cervical spine lateral radiographs with flexion and extension views should be obtained to exclude significant subluxation. Preoperative anesthesia consultation is mandatory in the RA patient with cervical instability. Fiberoptic intubation should be considered to limit neck manipulation.

SPINAL INVOLVEMENT IN THE SPONDYLOARTHRITIDES

Neurologic manifestations are common in spondyloarthritis (SPA), particularly in ankylosing spondylitis. In longstanding disease, the spine is rigid, fused, and brittle. Spinal fracture may occur spontaneously or with minimal trauma. A dreaded complication is cervical fracture, generally presented as acute neck pain, with or without neurologic compromise. Cord compression with quadriplegia may ensue unless the spine is promptly stabilized. Neurosurgical involvement is requisite. Ankylosing spondylitis may also be complicated by atlantoaxial subluxation, as in RA. Arachnoiditis may lead to scarring of sacral and lumbar nerve roots and cauda equina syndrome, with saddle anesthesia, paraparesis, and bowel and bladder disturbances.

AIRWAY INVOLVEMENT IN THE RHEUMATIC DISEASES

Airway involvement is a rare but significant source of morbidity and mortality in the rheumatic diseases. Granulomatosis with polyangitis (GPA, formerly Wegener granulomatosis) is a systemic vasculitis characterized by granulomatous inflammation of the upper and lower respiratory tract and glomerulonephritis. Vasculitic inflammation may occur in the subglottis and proximal trachea. Tracheobronchial GPA often does not respond to traditional systemic therapy and may run a course independent of the other manifestations of GPA, leading to recurrent infections or ventilatory obstruction. Tracheobronchial involvement should be suspected when a patient with known GPA presents with sore throat, cough, and difficulty with secretions. Chest radiography and spirometry are helpful initial tests, which may be confirmed with laryngoscopy or CT scan. When this complication is suspected, otolaryngologic consultation is mandated. Treatment involves intralesional steroid injection and dilatation of obstructive lesions. When severe, stenting and tracheostomy may be necessary.

Relapsing polychondritis (RP) is characterized by episodes of inflammation of the cartilaginous structures of the outer ear, nose, larynx, and tracheobronchial tree. Tracheobronchomalacia may result from the loss of the supporting cartilage of the upper airway, resulting in either fixed airway obstruction or hyperdynamic collapse. Concerning symptoms include progressive dyspnea, stridor, hoarseness, sore throat, and chest discomfort. The flow-volume loop is a useful screening test. It may reveal dynamic extrathoracic or intrathoracic obstruction, or both. This may be confirmed with bronchoscopy or inspiratory/expiratory CT scanning. Treatment options include stenting, balloon dilatation, or tracheostomy.

PULMONARY-RENAL SYNDROMES

Patients may present with both pulmonary infiltrates and renal insufficiency, and no obvious cardiac or infectious cause. This should raise consideration of several diseases leading to pulmonary-renal syndromes, especially when these patients have proteinuria or active urinary sediments to suggest glomerulonephritis. Pulmonary-renal syndromes may be immune complex-related, as in systemic lupus erythematosus (SLE) or cryoglobulinemia, or mediated by direct antibody binding, as in anti-glomerular basement membrane (anti-GBM) disease, also known as Goodpasture syndrome. Alternatively, pulmonary-renal syndromes may be pauci-immune, characterized by a relative lack of immunoglobulin and complement on histopathologic analysis. Pauci-immune conditions include the vasculitides associated with anti-neutrophilic cytoplasmic antibodies (ANCA), such as GPA, microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). Clinical clues may suggest a specific diagnosis. Patients with SLE may also have arthritis, pleurisy, and photosensitivity. Patients with ANCA vasculitis may have sinusitis, otitis, or mononeuritis multiplex.

Diagnostic evaluation in patients with pulmonary-renal syndrome should include testing for serum complement levels, ANCA, antinuclear antibodies (ANA), anti-GBM antibodies, and cryoglobulins. Use of cocaine contaminated with levamisole has been associated with a drug-induced ANCA vasculitis. Thus, it is prudent to include a toxicology screen for cocaine in patients presenting with an ANCA vasculitis syndrome. Biopsy of affected tissue (usually kidney) should be strongly considered for most patients presenting with pulmonary-renal syndromes. In the face of undifferentiated disease and clinical deterioration, empiric therapy including high-dose corticosteroids and even cyclophosphamide or rituximab may be necessary, pending the results of testing or biopsy.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) complicates a variety of rheumatic diseases including scleroderma, dermatomyositis/polymyositis (DM/PM), SLE, RA, Sjögren syndrome, and mixed connective tissue disease (MCTD). ILD affects up to 50% of patients with scleroderma, 30% of patients with DM/PM, and 10% of patients with RA. While parenchymal lung disease is often insidious, in some cases it may be explosive and require hospitalization. Patients may present with dry cough, progressive dyspnea, and desaturation with exercise oximetry.

High-resolution chest CT scan is useful in characterizing ILD. It may reveal ground glass opacities, seen in many other conditions including acute interstitial pneumonia, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, *Pneumocystis jiroveci* pneumonia (PCP), viral pneumonia, pulmonary edema, and acute respiratory distress syndrome. Honeycombing and traction bronchiectasis are seen in fibrotic lung disease and usual interstitial pneumonia, and consolidative inflammatory lung disease is seen in cryptogenic organizing pneumonia. However, there is much overlap in the radiographic appearance of different forms of ILD. Lung biopsy may be diagnostic, although the potential utility of a histopathologic diagnosis must be balanced against the hazards of lung biopsy in patients with tenuous respiratory status.

Treatment for inflammatory lung disease involves high-dose corticosteroids with immunomodulating agents such as cyclophosphamide, azathioprine, mycophenolate mofetil, or calcineurin inhibitors, such as cyclosporine and tacrolimus. Fibrotic lung disease may require lung transplantation in suitable patients. In patients with worsening respiratory symptoms already on immunosuppressive regimens, bronchoscopy should be strongly considered to exclude concurrent superimposed opportunistic infection. In patients on high-dose corticosteroids for ILD with or without a second agent, prophylaxis against PCP should be strongly considered.

VISION LOSS IN GIANT CELL ARTERITIS

Giant cell arteritis (GCA) is a large-vessel vasculitis that most often affects branches of the external carotid arteries. GCA must be recognized and treated promptly, as patients may suffer irreversible vision loss. Although patients may be as young as 50 years old, most are of age 60 or older. In addition, most patients are of Northern European ancestry. GCA is the most common systemic vasculitis in older adults, but it is still relatively rare. Among patients age 50 or older, incidence rates are reported at 20 to 30 cases per 100,000 patients in Northern European countries. GCA occurs at an even lower frequency in nonwhite patients, with estimates as low as 1 case per 100,000. *Temporal arteritis* is a term used to describe vasculitis of the temporal artery, which is common in GCA. Cranial symptoms of GCA include headache, scalp tenderness, jaw claudication, and visual disturbances. Involvement of the thoracic great vessels may cause upper-extremity claudication. Aortitis may manifest years after the initial diagnosis and treatment of GCA. Patients present with signs and symptoms of aortic aneurysm or dissection. GCA may sometimes present as a chronic cough, failure to thrive, and fever of unknown origin in an elderly patient. Most patients also experience fatigue, anorexia, and weight loss.

GCA may coexist with polymyalgia rheumatica (PMR), a condition that causes achiness and stiffness of the shoulder and hip girdle, worse in the morning, and associated with fatigue. Patients with established PMR have an approximately 10% risk of developing GCA at some point in their lives, even years after the diagnosis and treatment of PMR.

Ophthalmologic evaluation is mandatory in patients with suspected GCA. It may reveal evidence of anterior ischemic optic neuropathy, retinal artery occlusion, or choroidal infarction. The remainder of the physical examination may reveal subtle clues of arteritis. Tender, tortuous temporal arteries are a classic but unreliable finding. A chest bruit, aortic insufficiency murmur, or discrepant upper-extremity blood pressures signal thoracic vessel involvement. Patients with concurrent PMR may have bursitis of the shoulders and hips, with painful limited range of motion in these joints.

The diagnosis of GCA is based on the clinical presentation, with corroborative pathologic findings of arteritis. The temporal artery is the most easily accessible extracranial artery for biopsy. Temporal artery biopsy is a high-yield, low-risk procedure. There is an emerging role for arterial ultrasound in patients with suspected GCA, although this test does not replace the role of biopsy. There is no single blood test diagnostic for GCA. Markedly elevated acute-phase reactants are suggestive, but nonspecific. The erythrocyte sedimentation rate (ESR) may be as high as 100 mm/h, a value found in few other disease states (**Table 246-1**). However, normal acute phase reactants have been rarely reported in patients with GCA. Anemia of chronic disease and thrombocytosis may also be present.

TABLE 246-1

Select Conditions Associated with Erythrocyte Sedimentation Rate ≥100 mm/hour

Polymyalgia rheumatica
Giant cell arteritis and other vasculitides
Adult-onset Still's disease
Infectious endocarditis
Osteomyelitis
Septic arthritis
Multiple myeloma

Classification criteria exist for GCA (**Table 246-2**). These were designed primarily for use as inclusion criteria for research studies, rather than for everyday clinical practice. Certainly, there are patients with GCA who do not meet these criteria. The diagnosis of GCA should be considered in any elderly patient who presents with recent-onset headaches, visual complaints, and unexplained elevated acute phase reactants. In these instances, empiric corticosteroid treatment should be started *immediately*, and temporal artery biopsy should be arranged expeditiously. Empiric corticosteroids

do not alter pathologic findings, provided that the artery in question is sampled within 10 to 14 days of initiating treatment. Neither visual disturbances nor abnormal ophthalmologic exam need to be present to warrant immediate action. The retina is exquisitely sensitive to ischemia, and patients with GCA are unlikely to recover vision once it is lost. Treatment consists of corticosteroids in the equivalent of prednisone 1 mg/kg daily. Intravenous (pulse) corticosteroids have not been proven more effective for patients with GCA, but are an option for patients with threatened vision. Since luminal thrombosis of the ophthalmic artery is thought to be the event that precipitates blindness in GCA, low-dose aspirin may also be added to the therapeutic regimen. Once a patient starts treatment with corticosteroids, vision is often spared if it has not already been affected. Threatened vision is the most common emergency situation that may arise in GCA. In addition, aortitis may require emergent corticosteroids or even surgical intervention to reduce the risk of dissection or rupture. All cases of suspect or proven GCA warrant rheumatologic consultation for long-term management of disease.

TABLE 246-2

Classification Criteria for Giant Cell Arteritis

Age 50 or older
New-onset headache
Temporal artery tenderness
Erythrocyte sedimentation rate 50 mm/hour or greater
Histopathology showing arteritis

Classification of GCA is met if patient has three or more of the above criteria.

COMPLICATIONS OF SCLERODERMA

The term scleroderma encompasses both localized scleroderma (morphea or linear scleroderma) and systemic sclerosis. Localized scleroderma affects only the skin and is not discussed further here. In this chapter, the term *scleroderma* will be used interchangeably with the term *systemic sclerosis*. Scleroderma is characterized by autoimmunity, vasculopathy, and systemic fibrosis. Vascular complications include pulmonary hypertension, scleroderma renal crisis, cutaneous calcinosis, and telangiectasia of the skin or gastrointestinal (GI) tract. Progressive fibrosis may involve the skin, GI tract, lungs, heart, or other organs. This section focuses on two emergencies in patients with scleroderma: scleroderma renal crisis and Raynaud crisis (seen most often in, but not limited to, patients with scleroderma).

SCLERODERMA RENAL CRISIS

Scleroderma renal crisis (SRC) usually develops within 5 years of diagnosis of scleroderma. It may even be the presenting feature of scleroderma, often in patients with other signs of scleroderma that have eluded diagnosis, such as Raynaud syndrome, sclerodactyly, cutaneous fibrosis, organ fibrosis, and telangiectasia. Rapidly progressive skin disease and prior corticosteroid usage are major risk factors for renal crisis. SRC usually presents as hypertension and progressive renal insufficiency in a patient with scleroderma. Patients may have symptoms of malignant hypertension: headache, visual disturbances, pulmonary edema, and encephalopathy. Progression to hypertensive crisis, overt renal failure, and death is rapid without prompt recognition and treatment.

SRC is a microangiopathy of the renal vasculature, not a form of glomerulonephritis. Urinalysis may reveal proteinuria and hematuria, but red blood cell casts are typically absent. The renal vasculopathy causes endothelial shearing of erythrocytes that may be detected as a microangiopathic hemolytic anemia (MAHA), with schistocytes on peripheral blood smear analysis and mild thrombocytopenia. As SRC may be the presenting feature of scleroderma, it should always be considered part of the differential diagnosis in a patient with unexplained renal dysfunction and MAHA features (**Table 246-3**). Renal biopsy does not distinguish SRC from other microangiopathies, but it may be useful to exclude glomerulonephritis. Ultimately, the diagnosis of SRC is a clinical one based on progressive hypertension, renal dysfunction, proteinuria, and MAHA in a patient with systemic features of scleroderma.

TABLE 246-3

Causes of Microangiopathic Hemolytic Anemia with Renal Failure

Scleroderma renal crisis
Antiphospholipid antibody syndrome
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
Heparin-induced thrombocytopenia
Malignant hypertension
Diffuse intravascular coagulation
HELLP syndrome (**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets)
Transfusion reactions
Drugs (most often chemotherapeutic agents)

Angiotensin-converting enzyme (ACE) inhibitors are the mainstay of treatment. This is the only condition in which overt renal failure is treated with aggressive ACE inhibitor therapy, so one must have reasonable diagnostic certainty before initiating treatment. While any ACE inhibitor is likely to be effective, captopril has the largest body of supportive evidence, it is rapidly effective, and doses can be escalated rapidly. Enalapril has the advantage of intravenous dosing in exceptional circumstances. The goal of therapy should be normalization of blood pressure within a few days of starting treatment. This often requires hospitalization for close monitoring and dose adjustment of drugs. Often, serum creatinine values will lag in their improvement, and ACE inhibitor therapy should continue undeterred by rising creatinine values. There is far less experience with angiotensin receptor blockers (ARBs) in SRC, and ACE inhibitors should be used whenever possible. In patients with ACE-inhibitor-induced angioedema, allergy consultation should be sought for possible desensitization.

Despite these measures, upwards of 40% of patients with SRC require dialysis for progressive renal failure. Concurrent pulmonary or cardiac scleroderma often precludes renal transplantation for SRC-related end-stage renal disease. Notably, it is not unusual for renal function to recover in patients with SRC after months or even years of dialysis, provided that ACE inhibitor therapy is continued unabated. Even so, patients with SRC have a 5-year mortality rate that approaches 40%, mostly because SRC portends aggressive extrarenal scleroderma.

RAYNAUD CRISIS

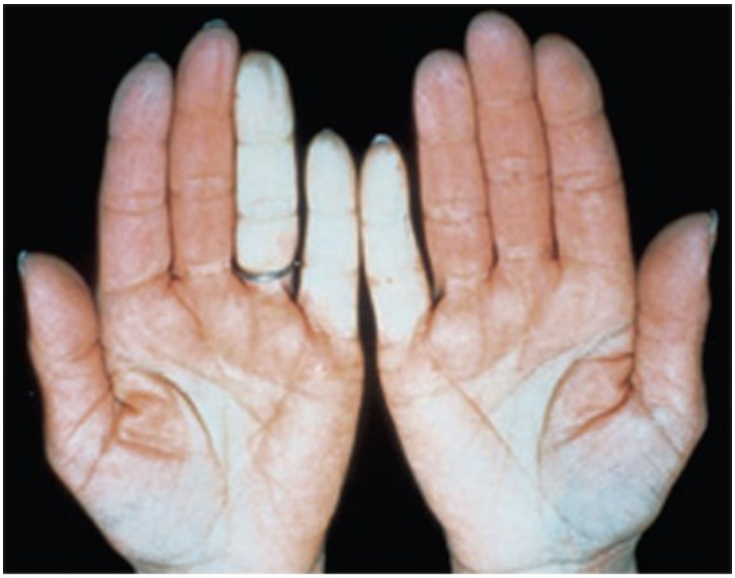
Primary Raynaud phenomenon (RP) is a common, usually benign, condition of cold-induced pain, pallor, and cyanosis of the digits, occurring in the absence of systemic connective tissue disease (CTD). Primary RP represents an exaggeration of normal physiologic vasoconstriction in response to cold. Secondary RP is a more aggressive version of RP that is associated with systemic CTDs like scleroderma, DM/PM, SLE, RA, Sjogren syndrome, and MCTD. A Raynaud crisis occurs when an episode of prolonged digital ischemia, lasting longer than 30 to 60 minutes despite rewarming, threatens the viability of one or more digits. It is a medical emergency that requires prompt intervention to reverse vasoconstriction and restore blood flow. Raynaud crisis most often complicates secondary Raynaud phenomenon, and not primary RP. Occurrence of a Raynaud crisis in a patient without known CTD should prompt a diagnostic workup for one.

Primary RP affects upwards of 10% to 20% of young women. It is much less common in men and the elderly. A typical episode involves a classic series of color changes. Digits first turn white in a demarcated fashion, as digital arteries vasoconstrict in response to cold (**Figure 246-2**). With prolonged vasoconstriction, digits become blue or purple because of tissue cyanosis. Finally, digits turn pinkish-red, as blood flow is restored, and the episode resolves. RP may also be triggered by stress or rapid changes in ambient air temperature, as upon entering an air-conditioned room on a warm day or reaching into a refrigerator or freezer. Of note, patient self-reporting of cold hands without color changes fails to satisfy the clinical diagnosis of RP. In patients with RP, episodes may involve all the digits or may be limited to a single digit (or part of a digit). Involved digits are often achy, numb, or even painful. Prolonged ischemia can lead to digital ulcerations or even a threatened digit.

Figure 246-2

Raynaud phenomenon, with digital pallor and cyanosis. (Reproduced, with permission, from Wolff K, Goldsmith LA, Katz SI, et al. *Fitzpatrick's*

Dermatology in General Medicine, 7th ed. New York, NY: McGraw-Hill; 2008. Fig. 171-1.)



Primary RP occurs in the absence of an underlying disease, and rarely has major sequelae. In contrast, secondary RP is associated with one or more of the conditions listed in **Table 246-4**. Many of these conditions are CTDs that are associated with vasculopathy and endothelial dysfunction. These factors contribute to the aggressiveness of secondary RP, which is more likely to produce severe symptoms, digital ulcers, or Raynaud crisis. Common drugs, such as caffeine, cocaine, amphetamines, pseudoephedrine, nicotine, and beta-blockers, can exacerbate arterial vascoconstriction in either primary or secondary RP. Patients with RP should be advised to avoid these drugs, and educated about signs and symptoms of a Raynaud crisis and the need to seek medical attention if it develops.

TABLE 246-4

Diseases and Conditions Associated with Secondary Raynaud Phenomenon

Category	Disease Entity
Rheumatologic diseases	Scleroderma
	Systemic lupus erythematosus
	Rheumatoid arthritis
	Sjögren syndrome
	Dermatomyositis/polymyositis
	Mixed connective tissue disease
	Vasculitis, including cryoglobulinemia
	Behçet disease
	Thromboangiitis obliterans
Other forms of vascular injury	Vibration-induced vasculopathy
	Radiation-induced vasculopathy
	Paraneoplastic vasculopathy
	Frostbite
	Drugs including chemotherapy and cocaine
	Ergotamines

PRACTICE POINT

- Acquired distal tubular acidosis is found in about 30% of patients with Sjögren syndrome, probably due to loss of the luminal H(+)ATPase pump from the intercalated cells of the collecting duct. This is clinically silent in most patients. However, it may sometimes lead to potassium wasting and weakness, and even be severe enough to present with hypokalemic paralysis, quadriparesis, and respiratory failure. The prognosis is good with aggressive potassium replacement in the short term and oral supplementation of potassium and bicarbonate in the long term.

History and physical examination is often sufficient to distinguish primary RP from secondary RP. In the absence of previously identified CTD, secondary RP is suggested by ischemic episodes lasting longer than 30 to 60 minutes, recurring RP isolated to a single digit, features of scleroderma, or pitting digital scars. Positive serologic tests for ANA or other autoantibodies and an abnormal nailfold capillary microscopy help to secure a CTD diagnosis. Nailfold capillary microscopy can be performed without special instruments. For example, an ophthalmoscope may be used to inspect a

nailbed that has been coated with a drop of mineral oil or even a clear bactericidal hand cleanser. Abnormal findings include dilated capillary loops, tortuous vessels, hemorrhage, or vessel dropout.

Raynaud crisis must be distinguished from other causes of digital ischemia, such as vascular trauma, vasculitis, proximal vessel stenosis, thromboangiitis obliterans, antiphospholipid antibody syndrome, atherosclerosis, and microembolic disease. The Allen test may be used at the bedside to assess for patency of both radial and ulnar arteries. Examination of pulses with Doppler ultrasound may help exclude proximal vascular occlusion. In selected instances, magnetic resonance angiography or even traditional vascular angiography may be necessary to confirm that the arterial stricture is at the level of the digital arteries, and not more proximal. Even then, it may be difficult to exclude digital microemboli, and proximal sources of emboli may sometimes need to be sought.

The goal of management in a Raynaud crisis is to reduce vascular contractility and restore blood flow to ischemic digits. Patients should be kept in a warm, stress-free environment to minimize further vasomotor stimuli. Affected digits should be reheated in tepid water; hot water should be avoided, as it may further damage ischemic tissue. Oxygen levels should be optimized, bearing in mind that pulse oximetry of a digit affected by RP is unreliable. Narcotic analgesia may reduce vasoconstriction induced by pain. Aspirin and sometimes heparin may lessen the risk of thrombosis within vasospastic vessels. Antihypertensive agents are typically used for initial vasodilator therapy. Dihydropyridine-class calcium channel blockers, such as short-acting or extended-release nifedipine or amlodipine may be of some benefit, but hypotension may be dose-limiting. Alpha-blockade with prazosin or doxazosin is often more effective, but hypotension may also be problematic. Oral hydralazine and transdermal nitroglycerin placed proximal to the part of the extremity involved may provide temporary relief, but tachyphylaxis and rebound vasospasm may occur. Anesthesia consultation may be required for chemical block of sympathomimetic nerves locally or cervically. Endothelin receptor antagonists, such as bosentan and ambrisentan, improve the healing rate of digital ulcers in patients with RP, but their role in Raynaud crisis has not been definitively established. In severe, refractory cases, digital sympathectomy, epoprostenol infusions, or phosphodiesterase inhibitors such as sildenafil and botulinum toxin injections may be attempted with the help of consultant services. Despite these efforts, patients may still experience digital necrosis and require amputation; it is advisable to involve vascular surgery whenever a patient presents with a Raynaud crisis.

DRUG TOXICITY IN THE RHEUMATIC DISEASES

While *allopurinol* is a generally well-tolerated medication for hyperuricemia, it is occasionally associated with serious toxicity. Allopurinol hypersensitivity syndrome ranges from a minor rash to a life-threatening systemic illness, with features of toxic epidermal necrolysis or Stevens-Johnson syndrome. It typically starts several weeks after drug initiation. Risk factors include renal insufficiency and rapid dose-escalation of allopurinol. In addition to rash, allopurinol hypersensitivity may also feature fever, eosinophilia, and acute hepatitis. Renal insufficiency, while not a typical side effect of allopurinol, can be a feature of allopurinol hypersensitivity. Treatment of allopurinol hypersensitivity includes administration of corticosteroids and cessation of allopurinol. In minor cases, patients may be rechallenged with allopurinol, but only under the direction of a specialist. Rechallenge should be generally avoided in patients with a history of severe allopurinol hypersensitivity reaction. Allopurinol can also rarely cause a severe ANCA-positive vasculitis. This generally improves upon drug cessation, although some cases require treatment similar to the ANCA-associated vasculitides. Allopurinol also inhibits the metabolism of azathioprine and 6-mercaptopurine (6-MP), increasing the risk of toxicity from these agents. The combination of allopurinol and these agents should be avoided if possible; if not, azathioprine or 6-MP dosing should be reduced to 25% of normal when using these agents concomitantly, under the direction of specialists.

Methotrexate (MTX) is among the most commonly used immunosuppressive medications in rheumatology. Toxicity may involve liver, kidneys, mucous membranes, and, in less than 1% of cases, the lungs. Pulmonary toxicity associated with MTX usually presents in the first year of use, with dry cough, dyspnea, fever, and, in severe cases, hypoxemia and respiratory failure. Alveolar or interstitial infiltrates may be seen on chest radiography or CT, although imaging may be unrevealing early in the course. The differential diagnosis includes community-acquired pneumonia, opportunistic infection, and progressive ILD from the underlying rheumatic disease itself. Bronchoscopy or induced sputum is often necessary to exclude opportunistic infection. Treatment in mild cases entails cessation of MTX. Corticosteroids or other immunosuppressive therapies may be necessary in severe cases. MTX overdose, whether accidental or intentional, is potentially life-threatening because of bone marrow suppression, nephrotoxicity, and hepatotoxicity. Hemodialysis does not effectively clear MTX. Early recognition of MTX overdose is critical in order to initiate folinic acid as a rescue therapy.

Cyclophosphamide (CYP) is an alkylating agent frequently used in the treatment of vasculitis and severe lupus. Major side effects include neutropenia and lymphopenia, which may lead to severe immunosuppression and overwhelming infection, especially with opportunistic pathogens such as fungi and PCP. CYP may also cause hemorrhagic cystitis, and it increases the lifetime risk of urinary tract cancer. The dose should be adjusted in the elderly

and for renal function to avoid toxicity.

Azathioprine is a purine analogue used in a variety of rheumatic syndromes. It may cause severe neutropenia, infection, and transaminitis. Patients with low or absent activity of the enzyme that metabolizes azathioprine, thiopurine methyltransferase (TPMT), are at increased risk for cytopenias and other toxicities. Genetic testing for TPMT is available and often obtained in patients starting azathioprine. Azathioprine has a number of problematic drug interactions, including ACE inhibitors, allopurinol, and other immunosuppressive drugs. It should be dose-adjusted in the elderly and in those with renal insufficiency.

SUGGESTED READINGS

Brown KK. Rheumatoid lung disease. *Proc Am Thorac Soc.* 2007;4:443–448. [PubMed: 17684286]

Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum.* 2008;37:223–235. [PubMed: 17692364]

Denton CP, Lapadula G, Mouthon L, Muller-Ladner U. Renal complications and scleroderma renal crisis. *Rheumatology (Oxford)*. 2009;48(30):32–35. [PubMed: 19015145]

Ernst A, Rafeq S, Boiselle P, et al. Relapsing polychondritis and airway involvement. *Chest.* 2009;135:1024–1030. [PubMed: 19017885]

Fathi M, Vikgren J, Boijsen M, et al. Interstitial lung disease in polymyositis and dermatomyositis: longitudinal evaluation by pulmonary function and radiology. *Arthritis Rheum.* 2008;59:677–685. [PubMed: 18438901]

Hunder GG. Epidemiology of giant-cell arteritis. *Clevel Clin J Med.* 2002;69(2):79–82.

Kim DH, Hillibrand AS. Rheumatoid arthritis in the cervical spine. *J Am Acad Orthop Surg.* 2005;13:463–474. [PubMed: 16272271]

Krause ML, Cartin-Ceba R, Specks U, Peikert T. Update of diffuse alveolar hemorrhage and pulmonary vasculitis. *Immunol Allergy Clin North Am*. 2012;32:587–600. [PubMed: 23102067]

Mouthon L, Bussone G, Berezné A, et al. Scleroderma renal crisis. *J Rheumatol*. 2014;41:1040–1048. [PubMed: 24833760]

Specks U. Diffuse alveolar hemorrhage syndromes. *Curr Opin Rheumatol.* 2001;13:12–17. [PubMed: 11148710]

Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354:2655–2666. [PubMed: 16790698]

Weyand CM, Gorozny JJ. Giant cell arteritis and polymyalgia rheumatica. *N Engl J Med*. 2014;371:50–57. [PubMed: 24988557]