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Vasculitic Diseases and Prothrombotic States Contributing to Delayed Healing In Chronic Wounds

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Abstract

PURPOSE—Autoimmune diseases are a common cause of delayed wound healing and should be considered in patients with chronic wounds who do not respond to local wound care or who fail skin grafting in the absence of infection.

RECENT FINDINGS—Epidemiologic studies have shown that, of patients with chronic wounds evaluated in specialized wound healing clinics, 20–23% have autoimmune etiologies for their wounds including vasculitis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, pyoderma gangrenosum and other autoimmune diseases.

SUMMARY—In this article autoimmune diseases known to be associated with chronic wounds and delayed wound healing are reviewed and the importance of a multidisciplinary approach for patients with chronic wounds, with involvement of rheumatology and dermatology is highlighted. This approach allows for investigation of underlying systemic disease and improves clinical outcomes for many of these challenging patients.

Keywords

Chronic Wound; Vasculitis; Pyoderma Gangrenosum; Rheumatoid Arthritis; Lupus; Leg ulcer

Introduction

Chronic wounds are a major public health issue, affecting approximately 6.5 million people in the US with costs estimated at $25 billion per year (1). These wounds significantly impact mortality (2) psychosocial wellbeing and quality of life (3). While large epidemiologic studies show that up to 79.7% of leg ulcers have a vascular etiology (4) (venous, peripheral arterial disease or mixed), approximately 6.6% of patients presenting to a dermatology clinic with chronic wounds have associated autoimmune disease (5). Similar epidemiologic studies conducted in dedicated wound healing clinics have found that up to 20 – 23% of patients with chronic wounds have associated autoimmune diseases including vasculitis, rheumatoid

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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arthritis, scleroderma, systemic lupus erythematous, psoriasis, and pyoderma gangrenosum (4, 6).

Normal wound healing

In normal healing, wounds progress through four overlapping phases: hemostasis, inflammation, proliferation and remodeling in order to restore epithelial integrity (7). Chronic wounds however, are often arrested in the inflammatory phase (7) and are unable to transition to the proliferation phase with concurrent upregulation of angiogenesis and matrix deposition. Underlying systemic immune diseases can contribute to delayed wound healing and these diseases should be considered in chronic wounds that are arrested in the inflammatory phase. In this review, the autoimmune diseases and prothrombotic states that are known to be associated with delayed wound healing will be reviewed and the data to support along with data to support targeted biologic therapy for these patients will be discussed.

Overview of vasculitic wounds

Vasculitis is the term used to describe a group of diseases that cause inflammation in blood vessel walls. Inflammation results in damage to mural structures and compromises vascular integrity and luminal flow leading to downstream tissue injury. Vasculitis can cause skin ulceration and delayed wound healing. Types of cutaneous vasculitis may be classified into primary vasculitic diseases such as in polyarteritis nodosa, or secondary to another autoimmune disease such as rheumatoid arthritis (RA), scleroderma (SSc) or systemic lupus erythematosus (SLE). Vasculitides are also categorized according to the size of the vessels affected.

For the purposes of this review, causes of cutaneous ulceration related to secondary forms of vasculitis associated with autoimmune diseases including RA, SSc and SLE will be reviewed first. Primary vasculitides and vasculitides associated with infectious etiologies will next be discussed and finally the features of some of some of the vasculitis mimics and vasculopathic processes that should be considered when evaluating a patient with delayed wound healing will be reviewed.

Rheumatoid arthritis associated leg ulcers and rheumatoid vasculitis

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases affecting 1% of the population. Leg ulcers occur in approximately 4.4% of patients with rheumatoid arthritis (RA) (8). Wounds associated with RA are usually attributed to cutaneous vasculitis (9). An epidemiologic study from the Mayo Clinic found that ulcers occur at a rate of 1.8 leg ulcers per 100 person-years in a population of 813 rheumatoid arthritis patients followed for 9771 person-years (10). In this study, 6% of ulceration episodes ultimately required amputation and in the RA population leg ulcers were associated with increased mortality (HR 2.42; 95% CI:1.71, 3.42). Leg ulcers in this RA population were associated with age (HR 1.73 per 10 year increase; 95% CI: 1.47, 2.04), rheumatoid factor positivity (HR 1.63; 95% CI: 1.05, 2.53), presence of rheumatoid nodules (HR 2.14; 95% CI: 1.39, 3.31) and venous thromboembolism (HR 2.16; 95% CI: 1.07, 4.36).

While clinicians often delay escalating immunotherapy in patients with RA-associated leg ulcers due to concerns regarding risks of infection and delayed wound healing, this concern is not supported by evidence. Studies show that while glucocorticoids may predispose to skin fragility and thus serve as a risk factor for ulceration in patients with RA, more aggressive therapy for the underlying RA using disease modifying antirheumatic drugs (DMARD) and biologic agents such as TNF-α inhibtors and rituximab as treatment for RA associated leg ulcers is beneficial and often results in healing (8, 11–13). In a large series investigating postoperative wound dehiscence in surgical patients, prior use of steroids or immunosuppressive drugs in the 100 days prior to the index surgery was not a risk factor for post-operative wound dehiscence (14) suggesting that steroid therapy may not be a direct risk factor for wound development. The association between steroid use and chronic wounds in RA patients is more likely related to the known association between RA severity and ulceration, since patients with more advanced disease, and thus predisposed to vasculitic wounds, are more likely to be on chronic corticosteroids (10). In patients with leg ulcers and underlying RA, referral to rheumatology and evaluation for escalation of RA therapy is warranted.

Systemic Lupus Erythematosus

Up to 5.6% of patients with systemic lupus erythematosus (SLE)(15) develop leg ulceration (16). In a study of 340 patients with chronic wounds evaluated in a tertiary wound center, 2.6% had underlying SLE (compared to a reported SLE prevalence of 0.05–0.15% in the general population, $p<0.001$) (6). Similar to RA-associated leg ulcers, ulceration in lupus patients may be secondary to immune complex mediated vasculitis. Histologic examination of wounds in SLE shows a leukocytoclastic vasculitis with fibrinoid necrosis of the vessel wall and prominent polymorphonuclear cell infiltration. Coexistent prothrombotic states such as antiphospholipid syndrome may also play a role in some patients (17, 18) and thromboocclusive histologic findings should prompt additional work up (5). Treatment of wounds in patients with SLE should focus on the management of the underlying autoimmune and inflammatory disease. Active vasculitis requires aggressive therapy with corticosteroids and steroid sparing DMARD agents. Patients with coexistent prothrombotic states often additionally require anticoagulant therapy. Belimumab (Benlysta®, GSK, US) is a monoclonal antibody that inhibits the B-cell survival factor BLyS, which is thought to play a critical role in some patients with SLE. Studies of Belimumab have shown benefit in musculoskeletal and cutaneous manifestations of SLE (19).

Scleroderma and Mixed Connective Tissue Disease

Scleroderma is a rare autoimmune disease in which immune activation results in vasculopathy, fibroblast stimulation, and connective tissue fibrosis. Lower extremity ulcers are a known complication of longstanding scleroderma, affecting approximately 4% of patients and causing significant morbidity (20). The prevalence of scleroderma in patients with chronic wounds is 2.35% compared to 0.02% in the general population ($p<0.001$)(6). Histologically, fibrin occlusive vasculopathy with intimal thickening and some inflammation is seen (20). Scleroderma ulcers are bilateral in 70% of cases. Coexistent prothrombotic states contribute to ulceration in scleroderma and evaluation for antiphospholipid antibodies and genetic prothrombotic states is recommended. Furthermore, arterial and venous disease

can be seen in as many as 50% of scleroderma associated ulcers, therefore, vascular evaluation is recommended in all patients (21). While vascular interventions play a role in the management of distal ischemia in scleroderma, the long-term effectiveness of bypass surgery is limited due to small vessel vasculopathy and studies show high rates of graft failure and limb loss (22). Medical interventions focused on the vasculopathic etiology of scleroderma-associated digital ulcers include vasodilators such as calcium channel blockers, prostanoids and endothelin receptor antagonists.

Topical and systemic opioids are often used to address the severe pain patients experience with these vasculopathic ulcers but it should be noted that retrospective data on post-operative wound dehiscence (14) and longitudinal data from the Wound Healing and Etiology (WE-HEAL) Study has shown that in a more general population with wound issues, higher opioid exposure is associated with slower wound healing. For this reason, cautious dosing should be considered when utilizing opioids in patients with chronic wounds.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis resulting in cutaneous ulceration (23). Lesions typically develop rapidly, with ulceration of a pustule or bulla and development of necrotic borders, purulent drainage, surrounding inflammation and erythema. Classically, PG lesions exhibit pathergy, with increasing inflammation in response to surgical debridement or biopsy. Often an underlying systemic immune disease, such as inflammatory bowel disease, psoriasis, or ankylosing spondylitis, can be identified. PG has also been described in association with hematologic diseases including acute and chronic myelogenous leukemia, hairy cell leukemia, myelodysplasia and IgA monoclonal gammopathy. While there are no specific diagnostic tests, the diagnosis hinges on a typical history along with the finding of neutrophilic infiltration in the dermis, in the absence of infection. Cytokine drivers of PG have been recognized and treatment targeted at the underlying immune dysfunction in specific cases is recommended (24, 25).

ANCA Associated Vasculitis and leg ulceration

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides include Granulomatosis with polyangiitis (GPA, formerly known as Wegener’s Granulomatosis), Microscopic Polyangiitis (MPA), and the Churg-Strauss Syndrome (CSS). Vasculitic leg ulcers are reported in association with all three of these forms of systemic vasculitis, as well as other forms of systemic vasculitis (26, 27). In cases with negative serology, tissue biopsy is often helpful to confirm the diagnosis (26). Biopsy should include the subcuticular tissue and biopsy of early lesions is often most informative (28). Histologic findings include leukocytoclastic vasculitis with infiltration of arterioles and postcapillary venules by neutrophils undergoing degranulation and fragmentation. Fibrinoid necrosis of the involved vessels and involvement of medium and small arteries of the reticular dermis and fat helps confirm the diagnosis. Direct immunofluorescence is recommended to identify immunoglobulin and complement deposits. As with ulcers caused by other autoimmune etiologies, aggressive treatment of the underlying autoimmune disease often results in healing of the wound (27, 29). With the advent of B-cell depletion therapy for ANCA

associated vasculitis, several authors have reported successful treatment of vasculitic leg ulcers with rituximab (Rituxan®, Genentech) (29, 30).

Thromboangiitis Obliterans (Buerger's Disease)

Thromboangiitis obliterans (Buerger's Disease) is a non-atherosclerotic, segmental inflammatory occlusive disease of small to medium sized arteries and veins, most often triggered by exposure to cigarette smoke. The disease may affect arteries and veins of the arms, hands, legs, and feet (31). Ischemia typically starts distally with later progression to ischemia of more proximal arteries. The presenting symptom is usually claudication of the extremities, but rest pain and ischemic ulceration can develop (31). Other presenting symptoms include splinter hemorrhages, Raynaud's phenomenon, or livedo reticularis.

Unlike most of the autoimmune diseases, Buerger's disease affects men more commonly than women and is strongly associated with cigarette smoking. The prevalence of Buerger's disease among patients with peripheral arterial disease ranges from as low as 0.5–5.6% in Western Europe, to as high as 45–63% in India, and up to 80% in the Jewish population of Ashkenazi ancestry living in Israel. Buerger's disease should be considered in any patient with critical limb ischemia under the age of 50. It should be noted that scleroderma can sometimes cause vasculopathy without skin changes, referred to as scleroderma sine scleroderma, serologic work up as outlined in table 1 allows other etiologies to be excluded.

In contrast to other forms of vasculitis, pathologic specimens in Buerger's disease show highly cellular inflammatory occlusive thrombosis, but relative sparing of the blood vessel wall and internal elastic lamina. Acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually normal and serologic markers and autoantibodies are typically negative (31).

Angiographic features of Buerger's disease include distal segmental occlusive lesions interspersed with normal appearing arteries, with areas of collateralization around the occlusions termed "corkscrew collaterals". Typically, the disease is infrapopliteral in the lower extremities and distal to the brachial artery in the upper extremities. Proximal atherosclerotic lesions are usually absent. It should be noted that the segmental occlusive disease seen in Buerger's can also be seen in the autoimmune and vasculitic diseases described above, including RA, Scleroderma and SLE, so these diseases should be ruled out serologically before attributing lesions to Buerger's disease (31).

Although smoking appears to be a major inciting factor in Buerger's disease, the pathologic mechanisms underlying this condition remain unclear. It has been postulated that smoking may cause delayed hypersensitivity or toxic angiitis. An association between periodontitis and smoking has been found, and bacterial DNA has been detected in the thrombotic samples. Others have postulated a role for endothelial cell antibodies in the pathogenesis of this disease and impaired endothelium-dependent vasodilation in the peripheral vasculature (31).

The mainstay of treatment for Buerger's disease is smoking cessation, which has been shown to reduce the risk of limb amputations and slow progression of the disease. Nicotine

replacement therapy should be used with caution and only as a bridge to smoking cessation since it can lead to ongoing tissue injury.

Infections associated with vasculitic and chronic wounds

Several chronic infections are associated with cutaneous ulcerations and should be included in the differential when evaluating a patient with a chronic wound who is not responding to usual therapy.

Hepatitis C can cause essential mixed cryoglobulinemia (Type II cryoglobulinemia), which can result in an immune complex mediated small to medium vessel vasculitis and ulceration. As with the ANCA-associated vasculitides, B-cell directed therapy with rituximab has shown to be an effective treatment for these patients (32). Treatment of the Hepatitis C using novel antiviral agents is also effective in these patients (33).

Hepatitis B is associated with polyarteritis nodosa (PAN) which can sometimes present with an isolated cutaneous vasculitis (34). While idiopathic PAN requires systemic immunosuppression, the mainstay of management of hepatitis B associated PAN involves antiviral therapy.Patients with chronic wounds that have not responded to usual therapy should be screened for hepatitis B and C as outlined in table 1.

Non-tuberculous mycobacteria can also cause chronic wounds. While first described in Africa as as the Buruli ulcer, these lesions can be seen in Australia and the US. If this diagnosis is being considered, it is imperative to request tissue biopsy with appropriate handling by the microbiology laboratory in order to ensure that the diagnosis can be made since atypical mycobacteria are slow growing and grow only under very specific culture conditions (35).

Erythema Nodosum and Panniculitis

Panniculitis is an inflammatory disease of subcutaneous adipose tissue that may result in induration and ulceration. Several pathologies can result in panniculitis of the lower extremities including nodular vasculitis, erythema nodosum, erythema induratum, pancreatic disease and α-1 antitrypsin deficiency (36).

Erythema induratum may present with tender nodules and plaques on the anterior or posterior calf that ulcerate and drain. These lesions are more common in young and middle aged women (36). Biopsy shows mixed septal and lobular inflammatory infiltrate with vasculitis. The differential diagnosis includes TB, Sarcoidosis and certain medications (e.g. sulfonamides and oral contraceptives).

Pancreatic panniculitis may develop in benign or malignant pancreatic disease. Patients present with painful subcutaneous nodules on the lower extremities and trunk that ulcerate with suppurative or oily drainage. Many patients have associated systemic symptoms including fever, abdominal pain, arthritis, ascites and pleural effusions. Histologic examination reveals septal and lobular inflammation along with characteristic “ghost cells” which are pathognomic for saponification of the adipose tissue seen in pancreatic panniculitis (36).

α-1 Antitrypsin deficiency is associated with neutrophilic panniculitis in which tender erythematous and purpuric nodules develop on the trunk and lower extremities. These lesions ulcerate and drain oily discharge, and result in scarring as they heal. Pathology shows neutrophilic infiltrate of the adipose tissue with necrosis and destruction of the fat lobules. Diagnosis is confirmed with serum α-1 antitrypsin activity and genotyping (36).

Sickle Cell Associated Leg Ulcers

Sickle Cell Disease (SCD) is an inherited hemoglobinopathy. Patients that are homozygous for hemoglobin S develop recurrent painful vaso-occlusive and hemolytic crises. Leg ulcers are a frequent complication of SCD and other hemoglobinopathies (37) affecting 2.5% of patients over 10 years old in the Cooperative Study of Sickle Cell Disease. Ulcer development is correlated with parameters of ongoing hemolysis such as low steady-state hemoglobin and high lactate dehydrogenase (LDH). Presence of HbF appears to be protective. This, combined with perfusion studies, suggests that ulceration in sickle cell disease may not be purely a vaso-occlusive process but more likely vasculopathy driven by an inflammatory state related to chronic hemolysis.

Hydroxyurea-associated leg ulcers

One of the most commonly used treatments for sickle cell disease is Hydroxyurea. Hydroxyurea is an antimetabolite that inhibits DNA repair by inhibiting ribonucleotide reductase and it is used in sickle cell disease to increase HbF production, thereby reducing the proportion of sickle hemoglobin. While Hydroxyurea is generally well tolerated, it is known to be associated with dermatologic side effects including alopecia, diffuse hyperpigmentation, erythema, skin atrophy, an amyopathic dermatomyositis, nail changes, poikilodermatous dermatitis, and resistant leg ulcers. Leg ulceration is seen in approximately 9% of patients receiving hydroxyurea in the setting of myeloproliferative syndromes and in approximately 29% of patients taking hydroxyurea for management of sickle cell anemia (38). This complication seems to be dose dependent, with studies reporting an association with a mean cumulative exposure to hydroxyurea of 3.2 (range 1.4 to 5.5) kg and mean duration of hydroxyurea treatment of 6.1 (range 2 to 15) years. Biopsy specimens have shown nonspecific changes, with one series reporting epidermal atrophy, dermal fibrosis, and occasional fibrin occlusive vasculopathy similar to that seen in livedoid vasculitis (39). The only effective therapy for these ulcers has been withdrawal of hydroxyurea (39, 40). In many cases, the underlying hematologic disease precludes this. However the introduction of oral janus kinase inhibitors for treatment of polycythemia has been successful in some patients (41).

Occlusive Diseases Resulting in Ulcers

Several diseases can be associated with occlusion of dermal vessels with thrombi or other occlusive material (such as cholesterol emboli or immune complexes). These ulcers are usually acute in onset and exquisitely painful but characteristically the patient has intact pulses. Careful evaluation including autoimmune and prothrombotic work-up as outlined in table 1 along with histopathology is recommended.

Atrophie Blanche or Livedoid Vasculopathy

Atrophie blanche or Livedoid Vasculopathy (LV) is a chronic small-vessel occlusive vasculopathy in which there are recurrent leg ulcers that heal with stellate porcelain white scars. Lesions are often bilateral, involving the dorsal ankle and foot. Atrophie blanche and LV is more common in women (42). Reported etiologies for LV include autoimmune diseases (43–51), hypercoagulable states and situations with impaired fibrinolysis (52). However, approximately one third of cases are idiopathic. On biopsy, characteristic pathologic findings include the presence of hyaline thrombi in the mid and upper dermal vessels with fibrinoid changes. In many cases, the characteristic skin lesions can be identified by clinical appearance and unless there is concern for other etiologies we rarely recommend biopsy since this can result in further issues with wound healing.

Cholesterol Emboli

Cholesterol emboli should be considered as a potential explanation for leg ulceration in patients with recent history of endovascular procedures. Patients present acutely with painful livedo reticularis and gangrene of a digit or limb – a syndrome commonly referred to as “blue toe syndrome” (53, 54). This syndrome is more common in men over 50 with atherosclerosis and often there is a history of recent (hours to days) arterial manipulation. The syndrome is also described as being precipitated by initiation of anticoagulation; however, this relationship has not been well delineated. Histopathology of affected skin and tissue demonstrates elongated cholesterol-clefts in the deep dermal arterioles. However, it is important to specifically ask pathologists to search for this finding in biopsy specimens if this diagnosis is being considered. The mortality of cholesterol emboli syndrome is high. Treatment includes removal or stenting of unstable atheromatous plaques as well as initiation of statins (17).

Calciphylaxis

Calciphylaxis refers to the calcific uremic arteriolopathy seen in patients with renal failure. It results in progressive occlusion of dermal vessels and manifests with acutely painful, indurated plaques that develop necrosis and ulceration. Calciphylaxis carries a poor prognosis with less than 50% 1 year survival (55). Diagnosis requires full thickness biopsy of an involved region, and the histopathologic finding of calcium deposition in the media of adipose vasculature is required to make the diagnosis. Peri-eccrine calcium deposition is a specific but not sensitive finding. Treatments focused on surgical wound debridement and lowering the calcium-phosphate product have some benefit, but parathyroidectomy is generally not effective. Numerous other treatments including sodium thiosulphate have been tried for this condition but with conflicting results (56, 57).

Cryoglobulin

Cryoglobulins are immune complexes that precipitate at temperatures below 37°C. There are several types. Type I cryoglobulins are usually IgM class and are associated with hematologic malignancies such as Waldenstroms macroglobulinemia and multiple myeloma. Patients with this type of cryoglobulinemia develop symptoms of hyperviscosity and acral

purpura, especially in cold weather. Histopathologic examination shows bland hyaline thrombi or red cell occlusion of superficial dermal vessels.

Types II and III are mixed cryoglobulins, i.e. they are composed of monoclonal or polyclonal immunoglobulins, often with rheumatoid factor activity (recognizing the Fc portion of IgG). These types of cryoglobulins are associated with chronic viral infections (such as Hepatitis B, C and HIV) and with autoimmune diseases (lupus, RA, Sjogrens Syndrome). Both type II and III mixed cryoglobulinemia may present with cutaneous ulceration, and a prodrome of arthralgias, myalgias and fatigue. Cryoglobulins are easily missed unless blood is drawn into collection tubes that have been pre-warmed to 37°C without anticoagulants. After clotting at 37°C for one hour, the serum is then separated by centrifugation at 37°C and placed in a graduated (Wintrobe) tube at 4°C for three to five days to allow precipitation of the cryoglobulin.

Prothrombotic wounds

Antiphospholipid syndrome

Leg ulceration in conjunction with painful livedo reticularis, splinter hemorrhages, leg ulcers, superficial thrombophlebitis and focal ischemia should raise suspicion for antiphospholipid antibody syndrome (APLS). Antiphospholipid antibodies react with the phospholipid portion of the prothrombin activator complex resulting in occlusion of the small dermal vessels (58). Treatment with anticoagulants, particularly those with an anti-fibrinolytic action, is beneficial for healing of these lesions and prevents further thrombosis.

Genetic prothrombotic states

Genetic prothrombotic states and coagulopathies are a recognized comorbidity in young patients with leg ulcers (59) and patients with livedoid vasculopathy. Using a correlative animal model, we have been able to demonstrate the impact that these prothrombotic states have on skin graft failure (60). In patients with refractory chronic wounds genetic prothrombotic work-up (Table 1) is warranted, and evidence from small studies supports use of fibrinolytic agents and anticoagulation in patients with livedoid vasculopathy or other wounds with an associated prothrombotic state (61, 62).

Conclusions

Vasculitic and prothrombotic etiologies should be considered in patients with chronic wounds who do not respond to appropriate vascular intervention and wound management. A collaborative approach with the involvement of dermatology and rheumatology allows investigation for underlying systemic disease contributing to delayed wound healing in these cases. When vasculitis is in the differential diagnosis and a biopsy is planned, the team should be careful to include reticular dermis and subcutaneous tissue. A methodical approach with meticulous history and physical exam along with laboratory work-up (as outlined in Table 1) improves clinical outcomes for many of these challenging patients.

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Conflict of Interest

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Table 1

Recommended laboratory testing to investigate autoimmune and prothrombotic states in patients with chronic non-healing wounds.

Test	Disease detected
Anti-nuclear antibody	Systemic Lupus Erythematosus and other autoimmune diseases
Anti-Smith antibody	Systemic Lupus Erythematosus
Anti-dsDNA antibody	Systemic Lupus Erythematosus
Complement C3 **Complement C4**	Systemic Lupus Erythematosus (low in active disease)
Anti-Centromere antibody	Scleroderma
Anti-Scl70 antibody	Scleroderma
Anti-ribonuclear protein (RNP)	Mixed connective tissue disease
SSA and SSB antibodies	Sjogrens Syndrome
Rheumatoid Factor	Rheumatoid Arthritis
Anti-Cyclic Citrullinated Peptide	Rheumatoid Arthritis
Anti-neutrophil cytoplasmic antibodies	Granulomatosis with polyangiitis, Microscopic Polyangiitis, Eosinophilic granulomatosis with polyangiitis, Cocaine and Levamisole associated vasculitis
Anti-β2-glycoprotein I antibodies	Antiphospholipid syndrome
Anti-cardiolipin antibodies	Antiphospholipid syndrome
Lupus Anticoagulant	Antiphospholipid syndrome
Prothrombin gene mutation	Genetic prothrombotic state
Factor-V Leiden mutation	Genetic prothrombotic state
Plasminogen Activator Inhibitor	Genetic prothrombotic state
MTHFR mutation	Genetic prothrombotic state
Quantiferon gold	Tuberculosis exposure
HIV test	HIV
Hepatitis B and C	Hepatitis B and C