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VASCULITIS (L ESPINOZA, SECTION EDITOR)

Rheumatoid Vasculitis: A Diminishing Yet Devastating Menace

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Abstract
Purpose of Review Rheumatoid vasculitis (RV) is an unusual complication of long-standing rheumatoid arthritis, which is characterized by the development of necrotizing or leukocytoclastic vasculitis involving small or medium-sized vessels. In this review, we aim to provide an update on the epidemiology, pathogenesis, clinical presentation, and management of this challenging extra-articular manifestation.
Recent Findings RV is heterogenous in its clinical presentation depending on the organ and size of blood vessels involved. The most common organs involved are the skin and peripheral nerve. Based on recent population studies, the incidence has significantly decreased with early recognition and the advent of immunosuppressive drugs and biologics; however, the mortality rates remain high.
Summary RV remains a serious extra-articular manifestation of RA that needs to be promptly recognized and treated. No consensus is available on treatment, given the ongoing debate of whether the biologics can trigger or treat RV.

This article is part of the Topical Collection on *Vasculitis*

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Introduction

Rheumatoid vasculitis (RV) is an inflammatory disease affecting blood vessels directly in a patient with rheumatoid arthritis. It typically causes a severe injury to the affected blood vessels and involves most frequently small vessels but may also involve medium and large vessels. RV is usually seen in patients with long-standing, severe, seropositive, and often uncontrolled rheumatoid arthritis (RA) and, although rare, is associated with significant morbidity and mortality. In this manuscript, we review the pathogenesis, pathophysiology, epidemiology, clinical diagnosis, and treatment of RV with primary focus on the clinical aspects of the disease.

Background

It is well accepted that RV is seen almost exclusively in seropositive patients in association with long-standing and severe disease, but it remains unclear which of these patients are at higher risk for development of RV and which and if any genetic marker increases the risk [1, 2]. The pathogenesis and pathology of RV is similar to other well-known systemic vasculitides with occurrence of both immune complex-mediated and cytotoxic processes. This leads to vessel wall inflammation, injury, necrosis, thrombus formation, and tissue ischemia. With the advent of biologics and aggressive therapy for RA leading to a better control, RV is seen far less frequently than before and there has been a decline in its prevalence; however, its cost and disease burden remain high [1]. Early

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recognition and treatment of RV is very important as it causes a substantial additional morbidity and can be fatal if left unchecked [3]. RV requires aggressive immunosuppressive, biologic, and perhaps cytotoxic therapy in some patients.

There are several other aspects of the disease, which remain unexplained such as what are the precipitating factors for development of the blood vessel inflammation and why the majority of the patients at risk do not develop a systemic vasculitis despite having severe, aggressive RA? What is the role of other lifestyle or genetic risk factors? Also, not known is, why in some cases, it is an isolated small vessel process and in others, a combination of both small and medium vessel vasculitis or isolated medium vessel or large vessel disease? A relationship between RV and other forms of blood vessel disease, i.e., atherosclerotic vascular disease, also remains unclear.

Pathogenesis

Immune complex deposition and activation of the complement system are felt to have a key role in the pathogenesis of RV [4]. Patients with RV typically have high levels of rheumatoid factor and low complement levels, supporting this.

Cellular adhesion molecules and TNF alpha may also have a contribution to pathogenesis. In a study by Flipo et al., labial salivary gland expression was examined in RA patients. There was found to be significant expression of ICAM-1, E-selectin, and TNF alpha in patients with active RV, but not in RA patients without vasculitis [5].

$CD4^{+}CD28^{null}$ T cells, which are uncommon in healthy individuals, have been implicated in vascular injury. It has been noted that patients with extra-articular involvement in RA, including vasculitis, have a high frequency of $CD4^{+}CD28^{null}$ T cells, which contribute to inflammatory lesions [6]. In addition, the *KIR2DS2* (killer cell immunoglobulin-like receptor) gene has been found to be enriched among patients with RV compared with normal individuals and RA patients without vasculitis, and together with the appropriate HLA-C ligand, this gene is felt to play a role in vascular injury by regulating $CD4^{+}CD28^{null}$ T cells [7].

Glucocorticoids and viral infections have been suggested as possible triggers for RV, but evidence is lacking. Smoking, however, has been shown to be a risk factor, and it is postulated that the mechanism involves immunomodulatory effects, including B cell- and T cell-mediated damage to the arterial intima, endothelial dysfunction, and possibly alterations in the function of the p53 gene, which regulates cell growth [8••, 9].

The HLA-DRB1 shared epitope genotypes *0401/*0401, *0401/*0404, and *0101/*0401 appear to be associated with the development of RV [10]; in patients lacking HLA-DRB1*04 shared epitope alleles, HLA-C3 has been implicated [11].

Epidemiology

Males appear to be at higher risk than females for RV, as well as older individuals with long-standing disease [4, 12]. In a large recent retrospective (case-control study) review of 86 patients with RV by Makol et al., it was noted that patients with evidence of severe disease such as nodules, history of joint surgery, and radiographic erosions had double the odds ratio of RV [8••]. The study also noted that coexisting vascular disease increased the risk of RV; the use of biologic drugs was also associated with a higher risk of RV; however, this may simply reflect more severe disease to begin with. In the same study, hydroxychloroquine and low-dose aspirin were found to have a protective effect.

In recent years, vasculitis in RA patients has declined, and it has been suggested that this is due to more early and aggressive RA therapy, as well as declining rates of smoking [9, 12]. Using the Norfolk Vasculitis Register (NORVASC), Ntatsaki et al., estimated the annual incidence of 3.9 per million for 2001–2010 as compared to 9.1 per million for 1988–2000 [13••, 14]. Similarly, Bartels et al. found a decrease in incidence of RV among US veterans [1]. Another study in Olmsted County, MN, confirmed this finding; the 10-year cumulative incidence of RV, but not other extra-RA manifestations, was significantly lower in the 1995 to 2007 cohort (0.6%) than in the 1985 to 1994 cohort (3.6%) [15].

Clinical Features

Rheumatoid vasculitis has a heterogenous presentation as it can involve small and medium-sized vessels, in practically all organs. Most commonly involved organs are the skin, eye, peripheral nervous system, kidney, lung, gastrointestinal system, and central nervous system.

The skin is involved in 90% of the patients. Isolated nail fold infarcts are the most common manifestation without other features of systemic vasculitis and usually do not require aggressive therapy. Other presentations can be non-healing leg ulcers, palpable purpura, pyoderma gangrenosum, and digital ischemia with a predilection for the lower extremities (Fig. 1). Ulcers on the lower extremities characteristically occur on the dorsum of the foot or proximal to the ankle unlike ulcers secondary to atherosclerosis. The second most common organ involved is the peripheral nerve, with distal sensory and motor neuropathy, or more severe mononeuritis multiplex, which results from necrotizing or occlusive vasculitis of vasa nervorum.

Approximately 16% of patients with RV have ophthalmic manifestations [4]. Scleritis is common, but the most severe manifestation is peripheral ulcerative keratitis [16]. It is imperative to rule out local or systemic infections as the cause of PUK.

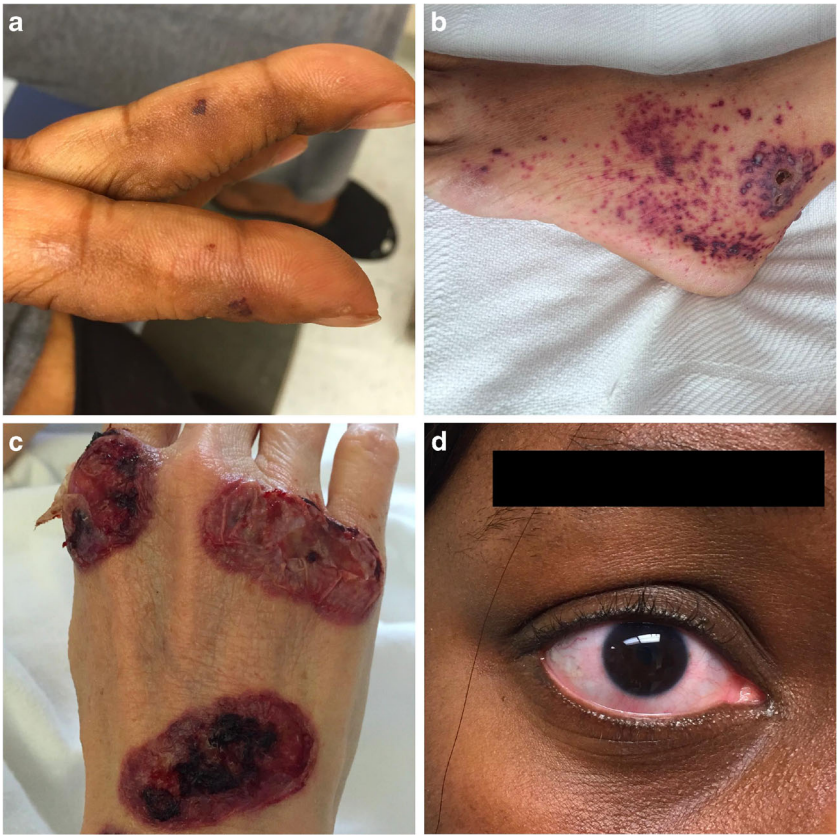

Fig. 1 **a** Small digital infarct in an RV patient. **b** Classic cluster of palpable purpura on the lower extremity in a patient with long-standing RA with low joint disease activity. Note the location of the purpura. **c** Pyoderma gangrenosum on the dorsum of the right hand in a patient with RA. Histopathology showed aggregation of neutrophils. **d** Scleritis in a patient with uncontrolled RA, characterized by hyperemia and deep, boring pain

Involvement of the lungs, kidneys, bowels, and CNS is rare but can be life threatening. Diffuse alveolar hemorrhage and pulmonary capillaritis can occur and mimic ANCA-associated vasculitis or Goodpasture syndrome. RV can also mimic polyarteritis nodosa causing mononeuritis multiplex, purpura, and gastrointestinal tract vasculitis, however without microaneurysms [17]. There are recent case reports of appendix, gallbladder, and testicular involvement [18–20].

Autopsy series and case reports suggest that both coronary arteritis and aortitis do occur in the context of RA: the distinction from atherosclerotic cardiovascular disease had been clinically impossible [5, 21–23]; however, in the NORVASC and Mayo Clinic registries, no cases of coronary angiitis were seen [8••, 13••]. Another common cardiac manifestation of RV is pericarditis.

Overall, the clinical presentation of RV in the recent studies is similar to that in prior studies. Patients with Felty syndrome (FS) are particularly prone to develop RV. In the recent reports, the prevalence of nodulosis and FS has declined, likely due to improved control of RA [8••]. This finding was also noted in the NORVASC registry, where the incidence of nail fold infarcts, nodules, and systemic manifestations had significantly dropped in the 2001–2010 cohort as compared to the 1988–2000 cohort [13••].

Table 1 illustrates the various presentations of RV based on organ involvement.

The occurrence of vasculitis was first reported in 1898 [24]. The concept of "burned out" disease has been validated in multiple studies wherein vasculitis develops when inflammatory arthritis is inactive and hence the joint exam is usually benign. It has been observed that vasculitis develops in RA patients who are seropositive and have destructive joint disease. The mean duration of the disease before the development of RV was 15.6 years as reported in the NORVASC registry and 10.8 years in the Mayo Clinic registry. There are multiple reports of development of vasculitis within 5 years of the onset of RA or sometimes even as the presenting manifestation of RA. Irrespective of when it occurs, it is associated with poor prognosis. Development of RV is associated with the male gender, extra-articular features, and the presence of severe RA requiring intensive therapy [2]. In the Mayo Clinic registry, one third of the cases were current smokers and one third had another extra-articular manifestation of RA [8••]. The median age at RV diagnosis was 63 years [8••].

Vasculitis is often preceded by constitutional symptoms and elevation of inflammatory markers. Patients usually have low disease activity but may continue to have extra-articular manifestations particularly rheumatoid nodulosis in 30% or Felty syndrome [25]. This is in contrast to lupus vasculitis where lupus flares go hand in hand with vasculitis [26]. A high titer of rheumatoid factor is usually present, but this is not an independent risk factor for development of RV [8••].

Table 1 Clinical features of RV based on organ system

Organ system	Presentation	Prevalence
Skin	Nail fold infarcts	90%
	Purpura	
	Non-healing ulcers	
	Digital ischemia	
	Livedo reticularis	
	Pyoderma gangrenosum	
	Rheumatoid nodules	
Peripheral nervous system	Sensory polyneuropathy	40%
	Motor polyneuropathy	
	Mixed polyneuropathy	
	Mononeuritis multiplex	
Eye	Scleritis	16%
	Episcleritis	
	Peripheral ulcerative keratitis	
	Retinal vasculitis	
Heart	Pericarditis	30%
	Coronary arteritis	
	Myocarditis	
	Aortitis	
Lung	Diffuse alveolar hemorrhage	Rare
	Pleuritis	
	Fibrosing alveolitis	
Kidney	Interstitial nephritis	Rare
	Pauci-immune GN	
	Testicular vasculitis	
Central nervous system	Seizures	Rare
	Strokes	
	Myelopathy	
	Hypertrophic meningitis	
	CN palsies	
Gastrointestinal involvement	Mesenteric vasculitis	10%
	Bowel ischemia	
	Arteritis of the liver, pancreas, spleen, appendix, and gallbladder	

In 1984, Scott and Bacon defined systemic RV in a patient with RA if there was one or more of the following: (a) mononeuritis multiplex, (b) peripheral gangrene, (c) biopsy evidence of acute necrotizing arteritis plus systemic illness (e.g., fever, weight loss), and (d) deep cutaneous ulcers or active extra-articular disease (e.g., pleurisy, pericarditis, scleritis) if associated with typical digital infarcts or biopsy evidence of vasculitis [27]. These criteria have not been validated but have been formalized recently [28].

Approach to Diagnosis of Rheumatoid Vasculitis

The diagnosis of RV is made based on the clinical presentation, laboratory tests, imaging studies where indicated, and if feasible tissue biopsy of the involved organ such as the skin, nerve, or muscle. Alternatively, an indirect confirmation can be obtained by detecting vasculitis in more accessible tissues like the muscle, skin, or rectal mucosa when CNS or GI involvement occurs. Histologically, RV involves small arteries, and all three layers of the vessel are infiltrated by neutrophils, lymphocytes, and plasma cells with features of vessel wall destruction. In lupus vasculitis, typically postcapillary venules are involved [29].

In an established seropositive RA patient, development of skin lesions or neuropathy should raise the suspicion of RV. It is important to assess the extent of organ involvement as this helps in identifying an accessible site with the highest yield for histopathological diagnosis and thus directs the need for aggressive therapy.

Laboratory studies are supportive but not diagnostic of RV. Upon presentation, patients typically have high inflammatory markers, thrombocytosis, anemia, and hypoalbuminemia. Hypocomplementemia and cryoglobulinemia may be present

and are otherwise not present in RA. Low levels of complement factor C4 are a negative prognostic marker [30]. RV patients often have positive rheumatoid factor and/or positive anti-citrullinated antibody. Absence of these antibodies confers a high negative predictive value for RV reaching up to 90% [31]. ANCA, in particular p-ANCA, is seen in 36–48% of patients with RV; however, they are often negative for MPO. p-ANCA is usually directed against the lactoferrin antigen [32].

Given the overlapping presentation with other connective tissue disease and infections, it is imperative to exclude other etiologies and thus may require extensive investigations. Histopathologic evidence of vasculitis is generally necessary for the diagnosis of RV. Skin biopsy is the least invasive and has a high yield [3]. Electromyography can confirm neuropathy; however, to determine the etiology, a nerve biopsy is often indicated. Mesenteric angiography is indicated when gastrointestinal involvement occurs to evaluate for microaneurysm, which is a feature of PAN. Early and accurate diagnosis is important to choose the appropriate treatment to control symptoms and prevent long-term damage [33].

Table 2 lists the necessary investigations required to establish the diagnosis of RV.

Table 2 Clinical evaluation in suspected rheumatoid vasculitis

Initial assessment
History and physical examination
Complete blood cell count with differential
Complete metabolic panel
Erythrocyte sedimentation rate
C-reactive protein
Urinalysis
Complement levels
Rheumatoid factor
Anti-cyclic citrullinated peptide
Cryoglobulin
Anti-neutrophil cytoplasmic antibody
Enzyme immunoassay PR3, MPO
Hepatitis panel
HIV
Immunoglobulin levels
Biopsy of the affected organ
Other tests as indicated for assessment of involved organs
Electrocardiography
Ophthalmologic evaluation
Nerve conduction study/electromyography
Mesenteric angiography
Computed tomography of the chest
Brain MRI with gadolinium and cerebrospinal fluid analysis

Differential Diagnosis

Petechiae and purpura on the lower extremities in RV cannot be differentiated from those seen in idiopathic thrombocytopenic purpura, hypersensitivity vasculitis, and Henoch-Schonlein purpura [33]. The most common cause of non-healing ulcers is atherosclerosis; however, the location, response to treatment, and, if necessary, a biopsy can differentiate it from RV. Use of biologics such as TNF inhibitors and tocilizumab has been associated with increased risk of RV, and thus, drug-induced vasculitis must be considered in the differential [8••, 34].

Other differentials to be considered include HBV-associated polyarteritis nodosa, HCV-associated cryoglobulinemia, HIV, and other infection-associated vasculitis [35]. Presence of c-ANCA or specific enzyme immunoassays such as MPO or PR3 should warrant investigation for AAV.

Treatment

There are no randomized controlled studies to assist in guiding treatment, and there is not an established consensus. Treatment of severe systemic RV typically involves high doses of corticosteroids and aggressive immunosuppression, frequently cyclophosphamide. Plasma exchange in RV has been used, but relapses may occur [36]. In a recent retrospective case-control study done at Mayo Clinic, involving 86 RV patients, one third of patients received high-dose corticosteroids and cyclophosphamide [8••]. In this study, other treatments included azathioprine, methotrexate, and mycophenolate mofetil, as well as biologic agents such as TNF inhibitors, rituximab, abatacept, and anakinra. Although there is concern regarding TNF inhibitors inducing vasculitis in some patients, it has successfully been used to treat RV. In a retrospective chart review published in 2008, complete remission using TNF inhibitors was achieved in five of nine cases (56%) of RV refractory to conventional immunosuppressive therapy [37]. Significant infections and relapses were seen however. Given the success in treating ANCA-associated vasculitis with rituximab, there is interest in using it in RV as well. In the Autoimmunity and Rituximab (AIR) Registry from France, 17 patients with RV were treated with rituximab; complete remission was achieved in 71% of patients at 6 months and 82% at 12 months [38•]. There is less information regarding the success of other biologics; however, there are case reports of successful treatment with abatacept and tocilizumab in RV [39–41].

Isolated nail fold vasculitis is thought to represent a less severe form of vasculitis. In a study from the UK in which 30 patients with nail fold vasculitis were followed and compared with 47 patients with systemic RV, there was little progression to systemic vasculitis in the patients with isolated nail fold changes, and therefore, aggressive treatment was not needed [42].

Treatment should be guided by the severity of involvement. Most of the time, RV will develop in an RA patient who is already on a DMARD, so escalation of therapy to a more

aggressive immunosuppressive is appropriate. For organ-threatening disease, this typically involves high-dose steroids and cyclophosphamide or consideration of biologic therapy, in particular rituximab. If the patient is already on a biologic and develops vasculitis, some consideration must be given to whether the biologic has contributed to vasculitis development [43•]. For patients with less severe manifestations, such as cutaneous disease or pericarditis, a less aggressive approach with oral DMARD therapy may be appropriate [44]. Finally, smoking cessation, blood pressure control, and local care of skin ulcerations are important adjunctive measures.

Prognosis

RV is associated with high morbidity and mortality. Of the 50 patients studied by Scott et al., recurrent disease was common and mortality was 30% [4]. In the retrospective case-control study from Mayo Clinic, 5-year mortality was 26% [8••]. In the NORVASC 2001–2010 RV cohort, 1-year mortality was 12% and 5-year mortality was 60%. In their prior 1988–2000 cohort, mortality was similar, demonstrating that despite a more aggressive approach to RA treatment, mortality for RV remains high [13••]. In the French AIR Registry cohort of RV patients, 88% sustained complete remission; however, the mean follow-up was only 33 months [38•].

Future Direction

Although the incidence of RV has decreased, mortality remains high. Most of the time, standard treatment involves aggressive therapy such as cyclophosphamide because of the seriousness of the condition. Biologic therapies, in particular B cell-depleting therapies, may offer promise for treatment with lower recurrence and mortality. Although TNF inhibitors have been successfully used to treat RV, there is concern that they can also precipitate vasculitis. Other biologic therapies, including abatacept and tocilizumab, are options, but there is little experience in RV with these therapies. Finally, the issue of whether hydroxychloroquine or low-dose aspirin may be protective needs to be explored as well.

Conclusion

Rheumatoid vasculitis, a serious complication of seropositive, severe rheumatoid arthritis, is associated with significant morbidity and mortality. Although most commonly involving the skin and peripheral nervous system, RV can affect a number of other end-organs including the heart, lungs, and kidneys. The incidence of RV continues to progressively decline with improvement in diagnosis and management of RA, but its prognosis remains poor due to lack of well-established treatment regimens. B cell-modifying therapies seem to hold the best promise in improving outcomes for moderate-severe RV. A high clinical suspicion is required to promptly recognize and aggressively treat this potentially fatal condition.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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