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Case Series
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Rheumatoid Vasculitis: A Case Series

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Abstract

Rheumatoid Vasculitis (RV) is a protean, destructive inflammatory process that is centered on the blood vessel wall and is associated with substantial morbidity. Although rare, it is the most serious extra-articular complication of Rheumatoid Arthritis (RA). Diverse and severe manifestations of this uncommon condition are a big diagnostic and management challenge. We describe a series of patients with the common diagnosis of RV, who received treatment and came for follow up in rheumatology inpatient department and vasculitis clinic of BSM Medical University, Dhaka. Studying these cases may help to develop insight into RV.

Introduction

The vasculitides are defined by the presence of inflammatory leukocytes in vessel walls with reactive damage to mural structures. The affected vessels vary in size, type, and location in association with the specific vasculitic disorder. Vasculitis may be localized to a single organ or vascular bed and may be clinically insignificant, but more commonly it is generalized [1]. It may occur as a primary process (primary vasculitides) or may be secondary to another underlying diseases [1], e.g., viral infections (HBV, HCV, HIV and others), systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis, Behçet's disease, and other connective tissue disorders. The presence of vasculitis should be considered in patients who present with systemic symptoms in combination with evidence of single and/or multi-organ dysfunction [2].

RV is a rare form of secondary vasculitis (the lifetime prevalence of RV among patients with RA was 2% in one large retrospective study, overall annual incidence being 3.4/million [3,4]). It is a serious complication of RA characterized by inflammation of small to medium-sized blood vessels, is associated with a particularly dire outcomes [5,6], with up to 40% of patients dying within 5 years due to damage from vasculitis and/or consequences of immunosuppressive therapy [7,8]. Vascular involvement in rheumatoid arthritis was first appreciated in 1898 in the works of Bannatyne [9], who described an inflammatory infiltrate within the vasa nervorum of a RA patient with peripheral neuropathy (PN).

RV can be clinically heterogeneous and can simultaneously affect multiple vascular beds. Clinical manifestations may include deep cutaneous ulcers, peripheral gangrene, vasculitic neuropathy, inflammatory eye disease and visceral infarction, all associated with poor outcomes. Long-standing RA, male sex, smoking, rheumatoid nodules, use of anti-TNF, have been associated with an increased risk of RV [10-12]. In Bangladesh, as far our knowledge is concerned, there is no systematic study on RV. The cases we studied had diverse clinical manifestation-ranging from common involvement of skin, digits, eyes, peripheral nervous system, to rare involvement of the cardiovascular system (coronary vasculitis) [13]. Study of this case series may help to elucidate different aspects of RV.

Case Series

Case 1

A 47-year-old man, normotensive, non-diabetic, smoker, presented with symmetrical deforming poly-arthritis for five years, low grade fever and digital gangrene (bilateral 2nd to 5th) for two months. He experienced acute high lateral myocardial infarction recently. Clinical examination revealed mild distal symmetric sensory neuropathy. His ESR and CRP were high, rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) were positive at high titers. Biopsy favored vasculitis. He was finally diagnosed as a case of RA, RV with digital gangrene, peripheral neuropathy (PN) and ischemic heart disease (IHD). He was managed with digital amputation and high dose glucocorticoid (HDGC), in the form of oral prednisolone (1 mg/kg/day), oral

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cyclophosphamide (CYC), followed by azathioprine (AZA). Other drugs- for secondary prophylaxis of MI, calcium, vitamin D, cotrimoxazole (for Pneumocystis jirovecii pneumonia prophylaxis) were also used. On follow up, there had been no recurrence of gangrene, and no infection. He was doing well with methotrexate (MTX) and leflunomide and occasional NSAIDs on demand basis.

Case 2

A 55-year-old normotensive, non-diabetic woman presented with symmetrical deforming poly-arthritis for nineteen years with gangrene in 1st and 2nd toes on both sides and in right little finger for two months. She had distal symmetric sensory impairment and developed scleromalacia perforans during hospital stay. She experienced auto-amputation of right 5th toe seven months earlier. Her ESR and CRP were high, RF and ACPA were positive at high titers. Biopsy was suggestive of vasculitis. Her final diagnosis was RA, RV with digital gangrene, PN, scleromalacia perforans. She was managed with digital amputation and HDGC, CYC followed by AZA and PJP prophylaxis. On follow up, no infection or recurrence of gangrene was observed, the eye involvement markedly reduced and stable. The RA activity was low and the patient was doing well with MTX.

Case 3

A 48-year-old hypertensive woman, with a solitary thyroid nodule presented with symmetrical poly-arthritis for 6 months, digital gangrene affecting left 1st, 2nd and 5th and right 2nd and 4th fingers and left little toe. She had Raynaud's phenomenon (RP) involving digits and toes. One examination, she had distal symmetric sensory impairment with wrist drop on the left and foot drop on the right side. Investigation showed high ESR and CRP, high titers of RF but negative ACPA. Peripheral blood film suggested leucoerythroblastic blood picture. Anti-phospholipid antibody (APL-Ab) was positive, histopathology was inconclusive, probably vasculitis. Her final diagnosis was hypertension, RA, RV with digital gangrene, PN (and positive APL antibody). She was treated with digital amputation, HDGC (oral prednisolone), CYC (oral), warfarin, aspirin, antihypertensive drug(s). We had diagnostic difficulties, as the duration of RA (6 months) was short, ACPA was negative, APL-Ab positive and Raynaud's phenomenon was present. An infection appeared at the amputated stumps during a follow up visit and CYC was discontinued, her neuropathy worsened. Ultimately, the patient died, probably due to overwhelming sepsis.

Case 4

A 55-year-old diabetic woman with coronary artery disease (post CABG status) and Cushingoid appearance presented with symmetrical poly-arthritis for twenty years, gangrene in the right thumb, middle, little and left small fingers and purpuric rashes on limbs and tingling numbness of distal extremities for two months. She became unable to walk for the last one month. One examination, she had digital gangrene, rash, bilateral wrist drop and foot drop and symmetric sensory poly-neuropathy. Investigation revealed, high ESR/CRP, high titer of RF and ACPA. Biopsy was in favor of vasculitis. Her complete diagnosis was DM, IHD, RA, RV with PN, digital gangrene and iatrogenic Cushing syndrome. She was treated with digital amputation, atorvastatin, antidiabetic, cardiovascular drugs, risedronate (anti-resorptive), calcium, vitamin D. As she had infection at amputated stumps, decisions on immunosuppressive and glucocorticoids were delayed expecting the infection to heal. Eventually she was lost from follow up.

Table 1: Clinical features and investigation of RV cases (n= 4).

Symptoms/signs	Number of patients	%
Neurological		
Generalized poly-neuropathy	4	100
Mononeuritis multiplex	2	50
Rheumatoin nodule	0	0
Cutaneous		
Purpura	1	25
Digital gangrene	4	100
Eye		
Scleromalacia perforans	1	25
Cardiac involvement		
Coronary vasculitis (?)	1	25
Infection		
At amputated stumps Investigation	2	50
RA $^{+ve}$	4	100
ACPA $^{+ve}$	3	75
Biopsy proven vasculitis	4	100
Duration, from diagnosis of RA to development of RV (%)		
≤ 5 years	> 5 years to 15 years	>15 years
2 (50%)	0	2 (50%)

Findings and Discussion

We studied a series of 4 patients who developed RV in course of RA. Three (out of 4) cases were female, although RV is more common in male [10,13]. All of them presented with digital gangrene and all had biopsy proven vasculitis. The duration from the diagnosis of RA to the onset of vasculitis is typically long; in one study, the mean duration from RA to RV was 13.6 years [13]. It was variable in the present series, 2 cases had long duration of RA before they developed vasculitis; one developed RV after 5 years; another 1 had surprisingly short duration (6 months) of joint symptoms before she develop RV. Unlike the common finding of Rheumatoid nodules (RN) in nearly all patients with RV [14], none in our series developed RN. All our cases had involvement of peripheral nervous system; two had mononeuritis multiplex (MNM). Although purpuric lesions are the most common findings of RV [15], only one of our patients had such lesions. Clinical features and investigations were shown in Table 1.

RA is a relatively common chronic inflammatory autoimmune disease that affects 0.5% to 1% of the adult population worldwide [16]. In addition to its joint manifestations, several organs and systems may be affected in RA, enabling the appearance of various extra-articular manifestations [17]; these manifestations are usually observed in individuals with high titers of RF and ACPA [18].

Unlike RA, which is relatively common, RV remains a rare entity. Incidence of RV has declined further in the past several decades, courtesy to the 'biologic era' [19]; but clinical presentation has remained unchanged and it continues to remain heterogeneous, similar to that reported in older case series [19-21].

RV classically occurs in patients with nodular, rheumatoid factor-positive, joint-destructive disease that has few clinical indications of active synovitis at the time the vasculitis begins, i.e., RV usually develops when the inflammatory arthritis is 'burnt out' [15]. RV

Table 2: Clinical presentation of rheumatoid vasculitis based on organ system involved [19].

Organ system	Clinical presentation
Skin (most common	Purpura, nail fold infarcts, digital ischemia/gangrene
	Cutaneous ulcers (upper or lower extremity)
Peripheral Nervous System(PNS)	Mononeuritis multiplex,
	Distal asymmetric/symmetric sensory and/or mixed
	Poly-neuropathy
Eye	Episcleritis,
	Scleritis (anterior/posterior, nodular/diffuse, non-necrotizing/necrotizing sclero-malaciaperforans)
	Peripheral ulcerative keratitis (with or without corneal melt)
	Retinal vasculitis
Heart	Pericarditis
	Myocarditis (presenting as arrhythmias–atrial fibrillation, ventricular arrhythmias and complete heart block)
	Coronary vasculitis (presenting as myocardial infarction)
Lung	Pulmonary angiitis/capillaritis (presenting as alveolar hemorrhage)
Kidneys	Pauci-immune glomerulonephritis
	Medium vessel vasculitis (without micro aneurysms)
Gastrointestinal tract	Mesenteric vasculitis
	Bowel (commonly ileal or sigmoid) and/or perforation
Central nervous system	Hypertrophic pachymeningitis
	Central nervous system vasculitis (presentations include seizures, cranial nerve palsies, strokes and myelopathy

Figure 1: RA, RV, and digital gangrene, PN (before and after treatment).

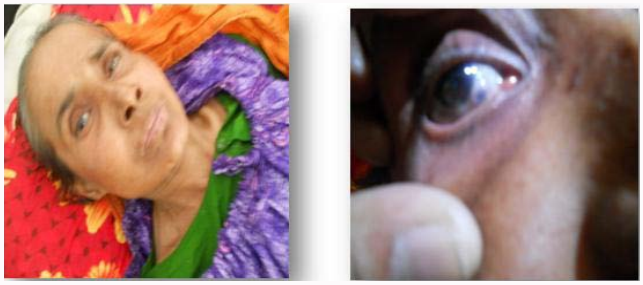

Figure 2: RV with digital gangrene with scleromalacia perforans.

typically affects small and medium-sized vessels, with associated sensory peripheral neuropathy (motor peripheral neuropathy often develops), deep cutaneous ulcers, digital gangrene, nail bed infarcts and palpable purpura. In one study, skin and peripheral nerve involvement were the most common manifestation in RV, followed by the involvement of eye and pericardium [19]. CNS vasculitis, mesenteric vasculitis, pulmonary angiitis, necrotizing glomerulonephritis are rare presentations.

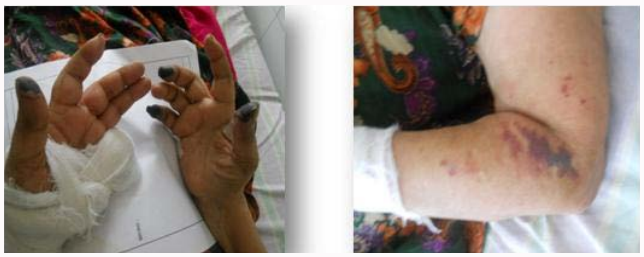

Figure 3: Digital gangrene and purpuric rash.

One of our cases (case 1), a 47-year-old male with a 10-pack year smoking history, developed MI during active RV. It was considered as a result of coronary vasculitis, since the patient was normotensive, non- diabetic with normal lipid profile and had no family history of premature coronary arterial disease. Although cases of coronary vasculitis are well-documented in the medical literature, myocardial infarctions that are the direct result of coronary arteritis in RV are rare [22-24].

According to 2012 CHCC (revised international Chapel Hill consensus conference nomenclature of vasculitides) RV fell under the category of 'Vasculitis associated with systemic disease'. There is no validated diagnostic or classification criteria for RV; Scott et al. [13], defined systemic rheumatoid vasculitis as one or more of the following in a patient with RA: First mononeuritis multiplex or peripheral neuropathy; second, peripheral gangrene; third, biopsy evidence of acute necrotizing arteritis with systemic illness (e.g., fever, weight loss), and finally deep cutaneous ulcers or active extra articular disease (e.g., pleurisy, pericarditis, scleritis). Other causes of such lesions, such as infection, atherosclerosis, trauma, arterial or venous insufficiency and diabetes mellitus, need to be excluded. All four cases in our series fulfilled these criteria.

Treatment of RV depends on the extent and the type of organ involved. Isolated nail fold vasculitis has a low risk for progression to systemic vasculitis and may be treated symptomatically without resorting to immunosuppressive therapy. Ulcerations due to RV may require treatment similar to that used for systemic involvement [25]. All patients with systemic RV (like all four cases in our series) require immunosuppressive therapy. Traditionally, HDGC (prednisolone with or without prior methyl prednisolone) and cyclophosphamide (CYC, pulse intravenous or oral) were the drugs for RV [13,26,27]. Some authorities [26] prefer a humanized anti-CD20 monoclonal antibody *viz*., rituximab ((375 mg/m^2 weekly times' four doses), in patients with severe RV, on the ground that rituximab may be safer than CYC. For patients who cannot tolerate or afford rituximab or for those who appear to be failing the regimen of rituximab and glucocorticoids, a combination of daily (oral) cyclophosphamide (up to 2 mg/kg per day, assuming normal renal function) and HDGC may be used. Azathioprine (approximately 2 mg/kg daily) may be used as maintenance therapy after inducing remission with CYC.

We used CYC and HDGC in three patients; clearly price of rituximab was the main concern for not using that drug. Two cases showed clear benefit, infection occurred in the other case and CYC was stopped (the patient died of overwhelming infection). In one study, infection and organ damage from active vasculitis were the leading causes of early death [19]. No immunosuppressive were used in one of our patients, because after amputation there had been infection at the amputated stumps.

What Seems New?

In the study of Makol et al. [19], a higher incidence of RV was observed in RA patients who also had co-morbidities like peripheral vascular disease (OR 3.98) and cerebrovascular disease (OR 6.48). Hydroxychloroquine and low-dose aspirin are associated with lower odds of developing RV, thus conferring a possible protective effect. Despite aggressive use of different DMARDs and biologics, RV continues to be characterized by high relapse rates and mortality that have not changed over decades. Although there seems to be a higher risk (OR 2.8) of development of RV with the use of biologics (especially anti-TNF), individual case review elucidated that, it was not the drug, rather the indication (severe base line disease), which was the confounding factor (Table 2).

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