acta medica

INVITED REVIEWS

Romatoid vasculitis: Definition based on Chapel Hill Conference Consensus 2012

Özlem Özdemir Işık[1], Ayten Yazıcı[1]

[1] Department of Internal Medicine, Division of Rheumatology, Kocaeli University, Faculty of Medicine, Kocaeli, Türkiye.

Corresponding Author: Özlem Özdemir Işık • E-mail: luska80@hotmail.com
This manuscript was peer-reviewed by Prof. Dr. Nazife Şule Yaşar Bilge

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease that progresses with synovial inflammation [1]. Rheumatoid vasculitis is a rarely seen but serious complication, observed especially in seropositive patients with long disease duration [2-4]. As RA's most severe extra-articular complication, rheumatoid vasculitis generally affects small and medium-diameter arteries and has high morbidity and mortality rates [5,6]. Although rheumatoid vasculitis can involve all organs, findings are most often seen in the form of skin and peripheral nervous system involvement. As there is no specific finding, the exclusion of other causes of vasculitis and the histopathological observation of necrotizing vasculitis is required for diagnosis [6,7].

Definition

In the Chapel-Hill consensus, rheumatoid vasculitis and systemic diseases are included in the secondary vasculitis group. According to this classification system, rheumatoid vasculitis should be considered in the presence of vasculitic lesions in patients with RA [8].

Classification

There are no validated diagnostic or classification criteria for rheumatoid vasculitis. Patients diagnosed with RA should have at least one of the 4 findings stated in the criteria recommended by Scott and Bacon in 1984, and other causes should be excluded. The findings in these criteria, which have not yet been validated, are as follows [3,6,9-11];

1. Mononeuritis multiplex or peripheral neuropathy
2. Peripheral gangrene
3. The biopsy finding of necrotizing arteritis accompanying systemic disease
4. Active extra-articular diseases such as pleuritis, pericarditis, and scleritis associated with biopsy findings of deep skin ulcers or typical digital infarct or vasculitis.

Epidemiology

Active vasculitis develops in approximately 1-5% of RA patients with disease duration longer than 10 years [4,6,10]. Cases have been reported at rates of 15%-31% in autopsy series [12]. However, it has also been reported that the incidence of rheumatoid vasculitis has decreased from 9.1 to 3.9 per million because of effective treatment modalities in the last 30 years. Many risk factors for rheumatoid vasculitis have been reported, including male gender, smoking, long duration of RA, rheumatoid nodules, and HLA class I and II genotype. Patients with Felty syndrome are known to tend to develop vasculitis [2,6,11,13-15].

Clinical Features

As many organs can be affected by rheumatoid vasculitis, which is the most serious complication

of RA, it can present with different findings. Unlike patients with lupus vasculitis, these patients have low disease activity. Extra-articular involvement, such as rheumatoid nodules and erosive disease, are present in patients. Skin involvement is the most common form, and there are skin findings in approximately 90% of cases. Petechiae, purpura, skin ulcers, and gangrene may be seen, and patients may also have general constitutional findings such as fever and weight loss [3,11,15-17]. In approximately half of the patients, peri and/or epineural arteritis associated with necrotizing vasculitis and associated acute, symmetrical, peripheral nerve lesions may develop. There may also be involvement of the heart, lungs, kidneys, gastrointestinal system, and central nervous system [3,4,10] (Table 1).

Diagnosis

It can be difficult to diagnose a patient presenting with findings of vasculitis if the diagnosis of RA is not known. The presence of skin lesions or neurological findings in a seropositive RA patient should be a warning in respect of rheumatoid vasculitis. The medical history, physical examination, laboratory tests, and histopathological examination may be necessary for diagnosis. Histopathological evaluation is important for diagnosis and the decision for aggressive treatment when necessary [3,6,11].

Although there is no specific laboratory test for the diagnosis of rheumatoid vasculitis, anti-cyclic citrullinated peptide (ACPA) positivity with RF at high titers, hypocomplementemia, and cryoglobulinemia may be detected in

Table 1. Clinical presentation of rheumatoid vasculitis [3]

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

most patients. In addition, findings supporting inflammation may be determined, such as acute phase reactant elevation, thrombocytosis, anemia, hypoalbuminemia, and hypergammaglobulinemia. Therefore, in addition to routine biochemistry, complete blood count, urine analysis, and acute phase reactants at the time of diagnosis, RF, ACPA, complement, and immunoglobulin levels should also be requested. To exclude other secondary vasculitis causes, hepatitis markers, anti-HIV, antinuclear antibodies, and anti-neutrophil cytoplasmic antibodies (ANCA) should also be examined. Moreover, it must not be forgotten that there may be perinuclear ANCA (generally lactoferrin) positivity in 36%-48% of patients with rheumatoid vasculitis [3,4,11,15].

In addition to the diagnosis, evaluation of the extent of organ involvement is important, and when necessary ophthalmological evaluation, electrocardiography, and electromyography should be performed [3,11].

Radiology: Depending on the organ involved in rheumatoid vasculitis, mesenteric angiography, thorax computed tomography (CT), or cranial magnetic resonance imaging (MRI) can be requested [3].

Pathology: Involvement of small to medium-diameter arteries is seen in rheumatoid vasculitis. Postcapillary venules are more often involved, and although IgG/IgM accumulation is usually seen, there may also be IgA accumulation. Postcapillary venules are more often involved than large vessels and are important in the differentiation of actual IgA or IgG/IgM vasculitis. Histopathologically, mononuclear cells, neutrophil infiltration in the vessel wall, and fibrinoid necrosis are determined. Findings of destruction, such as leukocytoclasis and necrosis in the vessel wall, are often observed [6,11,15,17].

Differential diagnosis

Other forms of vasculitis must be reviewed in the differential diagnosis of patients presenting with rheumatoid vasculitis. In patients presenting with skin findings such as purpura and petechiae in the lower extremities, a differential diagnosis should be made for idiopathic thrombocytopenic purpura, hypersensitivity vasculitis, and Henoch-Schönlein purpura and for patients with pulmonary, renal, and nervous system involvement, pulmonary-renal syndromes should be kept in mind, primarily ANCA-related vasculitis. As there are reports of rheumatoid vasculitis cases related to biological treatments such as anti-TNF and tocilizumab, patients must be evaluated in respect of drug-related vasculitis [3]. Another type of vasculitis involving small-medium diameter arteries is polyarteritis nodosa (PAN), which can sometimes be confused with rheumatoid vasculitis. In the differentiation from PAN, the observation of postcapillary venule involvement, RF positivity, and the presence of arthritis are important [6,17].

Management

In the literature, there are no randomized, controlled studies of rheumatoid vasculitis as it is rarely seen and there are no validated criteria. There are case reports and case series in which more empirical treatments have been given, and many treatments have been attempted including plasma exchange and IVIG. In patients with mild and moderate severity (rheumatoid vasculitis limited to the skin), treatment with disease-modifying anti-rheumatic drugs (DMARDs) such as moderate-dose steroid and methotrexate, azathioprine or leflunomide may be sufficient [3,10]. However, in cases with severe involvement, treatment is recommended of induction with cyclophosphamide in addition to high-dose steroids, followed by maintenance with DMARDs. Other biological treatments such as rituximab or anti-TNF agents, tocilizumab, and abatacept have been attempted in refractory patients, and positive results have been obtained [6,9,10,13,18].

Prognosis

Recurrence is common in rheumatoid vasculitis; the 5-year mortality rate has been reported to be between 30% and 60%. Disease-related complications and treatment-associated toxicity are among the causes that increase mortality [3,10,14].

CASE

Abstract:

Rheumatoid vasculitis is an uncommon long-term complication of rheumatoid arthritis. Although cases are often seen in the form of cutaneous

vasculitis, mononeuritis multiplex because of necrotizing vasculitis of vaso nervorum is also observed. Herein, a rheumatoid vasculitis case with mononeuritis multiplex is presented.

Case Presentation:

A 58-year-old male patient presented at the Neurology Outpatient Clinic with complaints of weakness in the legs. Complaints of pain and swelling in both hands' metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints started 10 years ago. At that time, morning stiffness lasted for approximately 1 hour. He was diagnosed as RA in another center and treatment was started with methotrexate (MTX) 15mg/week and methylprednisolone 4mg. Throughout the 10-year period, the patient had taken the drugs irregularly and had not attended regular follow-up appointments. In the last 2 years, the patient had taken steroids only and in the last 6 months, had taken MTX regularly. The complaints of weakness, pain, and numbness in the right lower extremity had started 1 month previously, and after 10 days, similar complaints developed in the left lower extremity. The patient was admitted to the Neurology Clinic.

On EMG, signal loss was determined at an advanced level in the bilateral peroneal nerves below the knee. On cervical spinal MRI, there was central-right paramedian protrusion not causing spinal canal pressure at the C4-C5 level, minimal diffuse bulging at C3-C4 and C5-C6 levels, and on lumbar spinal MRI, diffuse bulging and disc degeneration was determined at L4-L5 and L5-S1 levels, but no narrowing was determined in the spinal canal and neural foramen. The thorax CT examined in respect of malignancy was determined to be normal, and on the abdominal CT, stones were observed in the right kidney. On echocardiography, ejection fraction of 70%, left ventricle hypertrophy and relaxation impairment were determined, and normal left ventricle systolic functions.

Muscle-nerve biopsies were performed for the diagnosis of mononeuritis multiplex. In the nerve biopsy there was reported to be axonal degeneration in the nerve fibers, fibrinoid necrosis in the vascular structures of the nerve, and inflammatory cells such as neutrophils, lymphocytes, and histiocytes in the vessel wall. It was reported as necrotizing vasculitis and progressive axonal degeneration. Mononeuritis multiplex due to vasculitic neuropathy was considered by the neurology specialist so treatment was started with methylprednisolone 60 mg/day and gabapentin 300 mg/day. Our department was consulted and the patient was transferred to our clinic with the diagnosis of RA-related vasculitis. In the physical examination of the patient, swelling was observed in the 4th finger PIP joint of the right hand and in the 2nd, 3rd, 4th, and 5th finger PIP joints of the left hand. The proximal and distal muscle strength of the upper extremities were normal. However, the distal muscle strength of the lower extremities were 1/5 while the proximal sides were normal. In addition, decreased superficial and vibration senses in bilateral ankles, hypoesthesia in the distal lower extremities were detected. Deep tendon reflexes were normoactive and pathological reflexes were absent. Laboratory results: erythrocyte sedimentation rate: 65 mm/hr, C-reactive protein: 199 mg/dl, rheumatoid factor: 604 IU/ml, anti-CCP: 200 U/ml, anti-nuclear antibody (ANA): negative (-), ANCA: negative (-), EBV IgM (-), CMV IgM (-), Toxo IgM (-), HbsAg (-), anti HCV (-), anti HIV (-), VDRL (-), and the TSH, vitamin B12, and folic acid value were within normal limits.

The patient was treated with 1 gr cyclophosphamide because of vasculitis, and the steroid and gabapentin treatment were continued. The patient was referred to the Physical Therapy and Rehabilitation Department because of drop foot, was given bilateral plastic rest moulds, and underwent physical therapy rehabilitation, but the foot dorsiflexion and plantar flexion of the patient remained limited. After the completion of 6 cycles of cyclophosphamide treatment, the treatment was continued with azathioprine 150 mg/day, hydroxychloroquine 200 mg/day, and methylprednisolone 4 mg/day. As the joint complaints continued during the follow-up, leflunomide 20mg/day was added to the treatment. Under this treatment, the joint complaints recovered and there were no additional complaints. Until 2015, the patient attended follow-up visits irregularly, after which there was no follow-up. It was learned that the patient died because of COVID-19 infection in 2020.

Key Messages

- Rheumatoid vasculitis is the most severe extra-articular complication of RA and has high morbidity and mortality rates.
- Generally, small and medium sized arteries are affected.

– Although many organs are affected, skin involvement is most common.

– It is seen especially in male patients who are smokers with erosive disease of long duration

REFERENCES

[1] McInnes IB and Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-19.

[2] Turesson C, Matteson EL. Vasculitis in rheumatoid arthritis. Curr Opin Rheumatol 2009;21(1):35-40.

[3] Kishore S, Maher L, Majithia V. Rheumatoid Vasculitis: A Diminishing Yet Devastating Menace. Curr Rheumatol Rep. 2017;19(7):39.

[4] Cojocaru M, Cohocaru IM, Chico B. New insight into the rheumatoid vasculitis Rom J Intern Med. 2015;53(2):128-32.

[5] Helmick CG, Felson DT, Lawrence RC. et al. Estimates of the prevalence of arthritis and otherrheumatic conditions in the USA- Part I. Arthritis &Rheum.2008;58(1):15–25.

[6] Anwar MM, Tariq EF, Khan U, Zaheer M, Ijaz SH. Rheumatoid Vasculitis: Is It Always a Late Manifestation of Rheumatoid Arthritis? Cureus. 2019;11(9):e5790.

[7] Puéchal X, Said G, Hilliquin P, et al. Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis. A clinicopathologic and prognostic study of thirty-two patients. Arthritis Rheum. 1995;38:1618.

[8] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1-11.

[9] Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. Am J Med 1984;76(3):377–84

[10] de Cerqueira DPA, Pedreira ALS, de Cerqueira MG, Santiago MB. Biological therapy in rheumatoid vasculitis: a systematic review. Clin Rheumatol. 2021;40(5):1717-1724.

[11] Makol A, Matteson EL, Warrington KJ. Rheumatoid vasculitis: an update. Curr Opin Rheumatol 2015;27(1):63-70.

[12] Genta MS, Genta RM, Gabay C. Systemic rheumatoid vasculitis: a review. Semin Arthritis Rheum 2006 ;36:88–98.

[13] Coffey CM, Richter MD, Crowson CS, et al. Rituximab Therapy for Rituximab Systemic Rheumatoid Vasculitis: Indications, Outcomes, and Adverse Events. Rheumatol. 2020;47(4):518-523.

[14] Ntatsaki E, Mooney J, Scott DG, Watts RA. Systemic rheumatoid vasculitis in the era of modern immunosuppressive therapy. Rheumatology (Oxford). 2014;53(1):145-52.

[15] Radic M, Kaliterna DM, Radic J. Overview of vasculitis and vasculopathy in rheumatoid arthritis--something to think about. Clin Rheumatol. 2013 Jul;32(7):937-42.

[16] Watts RA, Mooney J, Lane SE, Scott DG. Rheumatoid vasculitis: becoming extinct? Rheumatology (Oxford). 2004;43(7):920-3.

[17] Sunderkötter CH, Zelger B, Chen KR. Et al. Nomenclature of Cutaneous Vasculitis: Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheumatol. 2018 Feb;70(2):171-184.

[18] Watts RA, Ntatsaki E. Refractory rheumatoid vasculitis-a therapeutic dilemma. Oxf Med Case Reports. 2016 Nov 24;2016(11):omw081.