Rheumatoid vasculitis

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Abstract

In rheumatoid arthritis joint involvement is sometimes accompanied by extra-articular features. These manifestations are exemplified by immune complex mediated vasculitis (rheumatoid vasculitis). Several different patterns may appear, none of them specific. Clinical manifestations are most frequently systemic, dermatological and neurological. Treatment is based on steroids, immune suppression, and sometimes, plasmapheresis. Prognosis is determined by the disease rheumatoid arthritis and not by the coexistence of rheumatoid vasculitis. Nevertheless, rheumatoid vasculitis is associated with a more aggressive form of rheumatoid arthritis.

Keywords: rheumatoid arthritis; rheumatoid vasculitis; extra particular features.

Rheumatoid arthritis (RA) is an auto-immune disease of unknown etiology, characterized by an erosive synovitis, sometimes associated with multisystem extra-articular manifestations, usually with inflammatory vascular lesions at their base.

The vascular lesions associated with RA have been known since the 19th Century. In 1898, Bannatyne described histological changes in the vasa nervorum;[1,2] however, it was only in the beginning of the 1950s that a relation between RA and vasculitis was established.[2] As a result, the concept of the disease was expanded; it is now considered a systemic disease (Bauer and Clark)[3] and the designation 'rheumatoid disease' was created (Ellman and Ball).[3]

All vessels can be affected in rheumatoid vasculitis (RV), but it is usually smaller vessels that are the most frequently affected, particularly the digital arteries, vasa nervorum and adjacent small veins.

Histologically, there are three types of lesions:[1,4]

1) necrotizing vasculitis,
2) non-necrotizing vasculitis, and
3) fibrous (or obliterating) endarteritis.

In necrotizing vasculitis, the existence of polymorphonuclear infiltrate is characteristic, with a prevalence of fibrinoid necrosis of the adventitia and media, and intimal edema, sometimes associated with intraluminal thrombus. The lesions evolve in sudden surges, with different stages of evolution existing together. On medium-sized vessels, the appearance of this type of vasculitis is the same as that found in polyarteritis nodosa.[1,2,4,5]

In non-necrotizing vasculitis, the inflammatory infiltrate is composed by lymphohistiocytic cells that surround the vessels, forming perivascular nodes or cuffs, associated with intimal thickening and sometimes, associated thrombosis.

Lastly, inflammatory infiltrate is not seen in the fibrous endarteritis, but rather, a subendothelial hyaline deposit that may extend to the media.

None of these three histological types is specific to RV, and all of them can occur, simultaneously or successively.[2,4,5] Their meaning is unknown, and different interpretations exist to explain this histological variability: for example, obliterating endarteritis is, for some authors, a cicatricial phase of a previous vasculitis, while for other authors it represents, when in isolation, an early vascular aging process.[1]

The observation of an immunological change, associated with the detection of immunoglobulin and complement deposits on the vessel walls, is evidence of the importance of the formation of circulating immune complexes in the pathophysiology of RV.[1,2,4,6,7,8]

A decrease in clearance capacity of these complexes by the reticuloendothelial system may eventually play a role in the development of vasculitis.[1]

IgG rheumatoid factors seem to be the most pathogenic factors, and their presence in high titers is strongly related to the development of vasculitis.[1,2,7] This association is explained by the strong antigen-antibody affinity demonstrated by this type of immunoglobulins, and their high capacity to activate

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TABLE I

Clinical manifestations in rheumatoid vasculitis

	Scott[2] (1981)	Vollertsen[10] (1986)	Wattiaux[1] (1987)
Systemic	82%	21%	65%
Peripheral neuropathy	42%	43%	60%
Skin	88%	50%	84%
Heart	34%	31%	38%
Eyes	16%	12%	19%
Lungs	34%	11%	10%
Kidneys	12%	11%	10%
Gastrointestinal	10%	4%	5%

the complement.[7,9]

The frequency of vascular involvement in RA varies according to the type of involvement, whether histological or clinical, and based on the rheumatoid population studied.

Investigations carried out in autopsies show the presence of histological lesions of vasculitis, which are not associated with clinical manifestations, in around 20% of the patients with RA.[1]

Clinically, RV is most frequently observed in hospitalized patients, initially with more severe disease, when compared to the overall cases of rheumatoid patients: it affects 6% to 10% of the patients of the first group and less than 1% in the remaining cases.[1]

Certain characteristics of rheumatoid disease appear to be related to the development of vasculitis.

In general, contrary to the RA, RV is most frequently observed in males, but the reason for this is unkown.[1,8,10]

RV is currently considered a manifestation that is within the clinical scope of rheumatoid disease, giving the disease greater severity.[8] Therefore, factors that define the characteristics of more severe RA will be associated with the development of vasculitis.[3,8,10] This group includes: 1) the existence of a high titer of serum rheumatoid factor; 2) the presence of subcutaneous nodules, periungual infarction or other extra-joint manifestation; 3) previous use of a greater number of disease-modifying drugs; 4) the need for corticosteroids and/or immunosuppressants to control the disease; 5) the existence of joint erosions.

There are various clinical manifestations of RV, and it can affect various organs or systems of the body (*Table 1*).

Skin manifestations are the most common clinical form of presentation, and occur in a large percentage of patients (in some series, more than 80% of the cases).[1,2]

Periungual infarcts are usually asymptomatic and fluctuating, and are generally associated with the presence of rheumatoid nodules. They are found in around 8% of all patients with RA, but when it is considered to RV, their incidence is higher (52% in Scott's series). Histologically, they are represented by a fibrous endarteritis similar to that found in scleroderma.[1]

Ischemic ulcers are common; according to some authors they occur in more than 80% of cases and tend to affect the lower limbs.[1,2] Vascular purpura, digital necrosis and maculopapular rashes are relatively frequently reported. On the other hand, erythema elevatum diutinum and pioderma gangrenosum are rare skin manifestations.[1,2]

The peripheral nervous system is affected in around 50% of cases; in terms of prognosis, we can distinguish two groups of peripheral neuropathy:[1,11] sensory distal neuropathy or distal neuropathy and sensorimotor mononeuropathy. Therefore, the first is associated with a favorable prognosis, while prognosis in the second group is, in general, more serious.[11]

TABLE II

Cutaneous signs in rheumatoid vasculitis

	Scott[2] (1981)	Vollertsen[10] (1986)	Wattiaux[1] (1987)
Purpura	25%	38%	50%
Gangrene	14%	42%	43%
Ulcers	56%	54%	19%
Livedo	-—	—	13%
Maculopapular rashes	10%	—	8%
Erythema elevatum diutinum	2%	—	5%
Pyoderma gangrenosum	2%	—	—
Periungual infarcts	52%	—	22%

Sensory distal neuropathy is characterized by the involvement of the extremities in a stocking-glove distribution, the frequency of which is difficult to estimate. It is represented by a clinical spectrum that includes infraclinical neuropathy, detected only by electromyography, or mild neurological changes.[1] The underlying structural changes include an axonal demyelination[11] and in terms of vascular aspects, some authors describe a necrotizing angiitis, identical to that found in panarteritis nodosa.[1]

Peripheral sensorimotor neuropathy and multiple mononeuropathy usually have an acute onset, are accompanied by axonal degeneration, and are frequently associated with extensive and serious necrotizing angiitis, in the context of systemic involvement.[1,11]

Systemic signs associated with RV include changes in general state of health, weight loss and fever. Its high frequency, higher than two thirds of cases in some case series, has led some authors to recommend that, in a patient with RA without evidence of joint involvement, the appearance of systemic signs lead to suspicion of RV, after ruling out infections and neoplasms.[2,12]

Other organs and systems are less frequently affected, such as the heart, large vessels, lungs, digestive system, eyes and kidneys.

All the layers of the heart can be affected, but only the involvement of coronary vessels seems to develop simultaneously with the other manifestations of RV.[1]

The presence of vasculitis, usually with no clinical relation, on the aortic root seems to be more common than expected, since investigations carried out in autopsies estimate that its frequency is approximately 1.5%.[1] The anatomical distributions and histological characteristics of the lesions seem to be identical to those observed in Ttyasu disease*, but the relation between both diseases is speculative only.[1]

Episcleritis and scleritis are characteristic eye manifestations and are frequently associated with other systemic manifestations, with the underlying etiopathogenesis being an immune mechanism. [1]

The involvement of the digestive system, with clinical symptoms, is rare. Nevertheless, when it occurs, it can be serious and can even lead to death.[1] The lesions affect small arteries, with ulcerations and subsequent hemorrhage and/or perforation, or larger arteries, with extensive segmental infarcts and intra-peritoneal hemorrhage.

Renal involvement in RV appears to be limited and its clinical expression generally includes proteinuria with or without hematuria.[1,2]

Pulmonary involvement in RV is represented by fibrosing alveolitis, secondary to vasculitis of the small arteries and responsible for pulmonary arterial hypertension, pleuritis, sometimes associated with pleural effusion, and intraparenchymal nodules. In Scott's case series, these manifestations occurred in 20%, 15% and 8% of the total patients with RV,[2] respectively.

The choice of therapy should always depend on the severity and extent of the vasculitis process. It is important to point out this aspect, since mortality may depend on a more aggressive initial treatment, or untimely immunosuppression.[5]

The literature in general considers a therapy regimen identical to that used for polyarteritis nodosa (not associated with viral hepatitis), i.e. corticosteroid therapy at high doses, possibly initiated by high doses of methylprednisolone, combined with an immunosuppressant.[5,13] The most frequently used immunosuppressant is cyclophosphamide, either orally or by intravenous bolus. There are several series showing the superiority of cyclophosphamide in the control of the manifestations of RV.[13] Nevertheless, for some authors, the combination of corticosteroids and azathioprine is equally effective as an initial treatment for RV.[14]

Plasmapheresis certainly has an important role in the control of acute RV; however, controlled trials are still needed to better define its indications.[5,15]

In terms of prognosis, contrary to what it is expected, the role of vasculitis as a determining factor of an unfavorable evolution has not yet been proven. Recent studies show that there is no significant increase in mortality in patients with RV when compared to a population of patients with severe RA without vasculitis.[16] In both groups, mortality at 5 years is around 30%,[2] which is significantly higher than the rates for the general population and patients with mild RA.[10,16]

The role of early administration of an aggressive therapy may perhaps explain the reduction in mortality that was high at the start.[16] Some authors emphasize the role of the indicators of severe RA in the overall prognosis of the disease, pointing out that RV is nothing more than an extreme form within the wide spectrum of manifestations that characterize rheumatoid disease.[3,4,8,16]

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