Small vessel multi-organ vasculitis and marantic endocarditis complicating rheumatoid arthritis

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Introduction
Rheumatoid vasculitis is an uncommon complication of rheumatoid arthritis (RA) with an annual incidence of 3.9 per million and results from the necrotizing inflammation of both small- and medium-sized vessels (1, 2). The disease typically occurs in individuals with severe, long-standing disease and is characterized by the presence of leukocytoclastic inflammation in affected tissue samples (1-3). As the latter is not unique to rheumatoid vasculitis, diagnosis depends on the correlation of clinical and serological findings while working to exclude other possible etiologies (1). Cardiac involvement with non-bacterial thrombotic (marantic) endocarditis is an extremely rare extra-articular complication of RA. As a disease entity, marantic endocarditis is uncommon, with most cases being attributed to underlying malignancy (4). To date, reported cases secondary to RA are limited (4, 5), and those described typically occurred in the absence of other systemic features of disease (6-8). Here, we report a rare case of marantic endocarditis secondary to RA in the context of fulminant vasculitic disease activity with multi-organ involvement.

Case Presentation
A 78-year-old lady presented with symptoms of headache, neck pain, nausea, and dizziness. She had a 15-year history of RA and a 7-year history of limited cutaneous vasculitis. Maintenance immunosuppression therapy consisted of methotrexate and prednisolone. On neurological examination at the time of presentation, only generalized weakness was identified. Initial investigations, including magnetic resonance imaging (MRI) of the brain, magnetic resonance angiography, a non-contrast MRI of the spine, and cerebral spinal fluid analysis, did not identify any causative pathology.

The patient was later discharged with some improvement in mobility. After 3 days, the patient was readmitted due to vomiting, pyrexia, and a rash affecting both legs. Key clinical findings at the time included vasculitic rash to both lower legs, systolic murmur, and acute confusional state. Empirical treatment for infective endocarditis was initiated. A subsequent transesophageal echo-cardiogram did not identify any vegetations, and antibiotics were stopped after 8 days. Serial blood and urine cultures yielded negative results. Viral serology and bacterial serology as part of screening for atypical bacterial infection were not sent. A computed tomography scan of the abdomen and pelvis, as well as a plain film chest radiograph, did not identify any causative pathology. The patient was later discharged with some improvement in mobility.

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The patient deteriorated further with acute kidney injury, nephrotic range proteinuria, fluctuating confusional state, deranged liver function, diarrhea, and frank hematuria. At the time, serum creatinine was 136 µmol/L, increasing from a baseline of 93 µmol/L. Protein-to-creatinine ratio was 717 mg/mmol with a serum albumin of 26 g/L. In view of this and recent MRI findings, small vessel vasculitis with renal and cerebral involvement was considered as the most probable diagnosis. Treatment with 1 g of intravenous...
methylprednisolone daily for 5 days was initiated, and care was transferred to the regional tertiary neurological center with renal support.

Immunology tests, including antinuclear antibody, antineutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane, anti-extractable nuclear antigen, antcardiolipin, and cryoglobulins were all negative. Immunoglobulins, serum electrophoresis, and complement were normal. At the time of transfer, erythrocyte sedimentation rate was 15 mm/h, and C-reactive protein was 44 mg/L.

Antineutrophil cytoplasmic antibody negative small vessel vasculitis was considered, and escalation of immunosuppressive treatment with cyclophosphamide was contemplated, but the patient remained extremely unwell for renal biopsy. Thereafter, the patient developed chest pain, and serum troponin level increased from 461 ng/L to 2178 ng/L over a 48-hour period. On transthoracic echocardiogram, hypokinetic anterior wall, septum, and apex with mild left ventricular systolic dysfunction were observed. Deterioration ensued from fluid overload and multi-organ dysfunction, compounded by presumed sepsis due to an acute rise in inflammatory markers that precluded any proposed immunosuppression. Active treatment was discontinued, and palliative care was commenced.

Post-mortem examination identified an organizing vegetation on the mitral valve leaflets, composed of fibrinous material (Figure 1). There were no organisms identified on Gram stain. The appearance supported non-bacterial thrombotic endocarditis. Additionally, there were minute hemorrhagic foci of epicarditis and evidence of coronary vasculitis with ongoing active inflammation of the endocardial vessels (Figure 2). Arteriosclerosis was present in all three main coronary vessels, but there were no critical stenosis, thrombosis, or ischemic changes in the myocardium.

Renal histology was strongly suggestive of renal vasculitis (Figure 3, 4) with progressive glomerulonephritis. Medium-sized arteries showed architectural damage with the disruption of elastic lamina, and smaller-sized vessels showed perivascular inflammation with nuclear debris. Fresh renal tissue was not available to perform immunofluorescence, and post-mortem renal tissue was inadequate for immunohistochemistry.

Findings in the small intestines were compatible with vasculitis affecting small- to medium-sized vessels (Figure 5). The brain demonstrated global atrophy with amyloid angiopathy, beta-amyloid plaques, and Lewy bodies. Intravascular fibrin thrombi were present at varying developmental stages at various locations, suggesting embolic manifestations (Figure 6). There were no significant features of sepsis on post-mortem examination.

**Main Points**
- Small vessel vasculitis can occur in the context of rheumatoid arthritis.
- Marantic endocarditis associated with rheumatoid vasculitis displays a tendency to affect the mitral valve with high risk of embolisation.
- Cerebral emboli secondary to marantic endocarditis should be considered as a potential cause of stroke in patients with rheumatoid arthritis.

**Discussion**
Here, we report a rare case of systemic rheumatoid vasculitis affecting the kidneys, intestines, and heart complicated by marantic endocarditis and cerebral emboli.

Rheumatoid vasculitis has a propensity to affect the skin and peripheral nervous system (1, 2, 9). Overall, the incidence of rheumatoid vasculitis has declined over the past 30 years from 7.9 to 3.9 per million, which is attributed to advances in immunosuppression therapy and more effective treatment strategies of RA (2, 3). Nevertheless, rheumatoid vasculitis causes significant morbidity and a higher mortality than RA, which remains unchanged despite improved therapy (2, 3).
In a retrospective study of 86 patients, necrotizing glomerulonephritis, mesenteric vasculitis, and endocarditis all remained a rare subset of rheumatoid vasculitis with an incidence of 1%, 2%, and 0%, respectively (9). The limited number of case reports that describe marantic endocarditis in this cohort all involved the mitral valve (6-8, 10), with one case also affecting the aortic valve (6). Lesions were characterized as either non-bacterial thrombotic endocarditis or rheumatoid nodules, but all cases described the presence of cerebral emboli (6-8, 10). Cases varied in their duration and severity of RA at presentation of rheumatoid vasculitis, with some occurring in the presence of quiescent articular disease (7, 8).

Currently, there is a paucity of data on how to treat systemic rheumatoid vasculitis. Treatment strategies rely upon evidence used to treat ANCA-associated vasculitis in the absence of clinical trials (2). Treatment varied between anticoagulation alone or with intensification of immunosuppression, typically with corticosteroids, in the identified case reports of marantic endocarditis secondary to RA (6-8).

The exceptional case described in this report is a rare example of systemic rheumatoid vasculitis with multi-organ disease and fulminant presentation. To our knowledge, this is the first case to be described in the literature.

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References