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Case Report

Can rheumatoid vasculitis predate a diagnosis of rheumatoid arthritis?

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Abstract

We report regarding a male patient who presented with a systemic vasculitis that was consistent with a diagnosis of polyarteritis nodosa. At presentation, he had no features of inflammatory arthritis but had a high rheumatoid factor titer and low C4 level. Withdrawal of immunosuppression after 6 years resulted in the development of classical rheumatoid arthritis (RA). This case supports previous reports that revealed that vasculitis may predate the development or occur very early in the course of articular RA.

Keywords: Rheumatoid arthritis, rheumatoid vasculitis, mononeuritis multiplex

Introduction

Rheumatoid vasculitis (RV) is a rare extra-articular manifestation of RA that usually occurs in the context of long-standing erosive disease. RV is associated with high morbidity and mortality, and depending on the site of vessel involvement, it can present with various clinical features, including leg ulcers, digit infarction, mononeuritis multiplex, scleritis, and generalized constitutional symptoms. A number of possible environmental and genetic predisposing factors have been identified, namely smoking, anti-CCP antibody positivity, and certain HLA alleles (e.g., HLA-DRB1-shared epitope genotypes) (1).

Vasculitis in early RA or preceding joint disease is extremely unusual and has only been described in a small number of case reports (2-4).

Case Presentation

A 38-year-old man presented to the Emergency Department of Wexham Park Hospital in Slough, UK with a 1-day history of right hand numbness and tingling of both hands. He had a history of generalized ill health for 4 months, which included generalized myalgia and arthralgia, weight loss, and recurrent episodes of testicular pain. The latter had been investigated with surgical testicular exploration; however, no abnormalities were identified. Therefore, he was discharged from surgical care.

Initial assessment revealed multiple splinter hemorrhages and a purpuric skin lesion on his left second toe. He was hypertensive with a blood pressure of 165/90 mmHg. Neurological examination revealed a sensory deficit in the distribution of his right ulnar nerve, left foot drop, and reduced sensation in both lower legs. He had no synovitis.

Initial laboratory studies showed anemia (Hb, 85 g/L), leukocytosis (12.1×10^9/L) with neutrophilia (9.3×10^9/L) and eosinophilia (0.9×10^9/L), elevated CRP level and ESR (76 mg/L and 41 mm/h, respectively), hypoalbuminemia (27 g/L), and normal renal and liver function. Immunological investigation results revealed high RF titers RF particle agglutination, 1280 IU/mL; normal range, 0–80 IU/mL), normal serum C3 levels but low C4 levels (1370 and 220 mg/L, respectively; normal ranges, 1050–2250 and 230–600 mg/L, respectively), negative for ANCA and cryoglobulins, and negative for hepatitis B and C and HIV serology. Imaging studies included normal transthoracic echocardiogram and normal CT visceral angiogram, which revealed no evidence of microaneurysms. Nerve conduction studies confirmed severe axonal mononeuritis multiplex, and sural nerve biopsy revealed perivascular and epineural inflammation, which was indicative of vasculitis.

Causes of elevated RF titers were considered. He had no evidence of inflammatory arthritis, infection screening was negative, and he had no other clinical features to support a diagnosis of connective tissue disease. Thus, a diagnosis of polyarteritis nodosa (PAN) was made on the basis of the findings of mononeu-

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ritis multiplex, cutaneous vasculitis, myalgia, testicular pain, hypertension, marked systemic upset, and weight loss. High-dose oral prednisolone (60 mg daily) and pulsed intravenous cyclophosphamide (Cytoxan; Baxter Healthcare Ltd, Norfolk, UK) treatments were initiated.

Over the next 12 months, his neurological symptoms gradually improved. He completed six cyclophosphamide cycles, and his oral prednisolone dose was slowly reduced. Azathioprine (Azamune; Juta Pharma GmbH, Flensburg, Germany) therapy was initiated at a dose of 150 mg daily, which was subsequently reduced over the course of 5 years to 50 mg daily. During this period, he remained asymptomatic.

Six years after his initial presentation, at the age of 44 years, he developed symmetrical inflammatory polyarthritis associated with elevated CRP levels of 79 mg/L and ESR of 80 mm/h. RF and anti-CCP antibody titers were significantly elevated (444 and 87 U/mL, respectively). According to the 2010 ACR-EULAR diagnostic criteria, he was diagnosed with rheumatoid arthritis (RA), and a reducing regimen of oral prednisolone in conjunction with methotrexate (Mercury Pharmaceuticals; London, UK) was initiated. He had no recurrent features of systemic vasculitis.

Discussion

In our case, the initial diagnosis was considered to be PAN. Our patient met six of the 10 criteria outlined in the ACR 1990 classification. However, two features favored a diagnosis of RV at presentation even in the absence of polyarthritis, i.e., a high serum RF titer and low serum C4 levels. In contrast, in idiopathic PAN, serum complement levels are usually normal, and RF is typically negative or weakly positive. RV and PAN share many clinical features and can be histologically indistinguishable. Unlike PAN, RV is not usually associated with the development of microaneurysms, and these were absent in our case's angiographic studies.

Managing RV depends on the type, distribution, and extent of organ damage. While limited cutaneous disease may respond to a lesser degree of immunosuppression, systemic RV is associated with a poor prognosis and warrants treatment with high glucocorticoid doses in combination with cyclophosphamide (5) or rituximab (6-7). Maintenance therapy consists of a switch to azathioprine in the case of initial cyclophosphamide induction or further cycles of rituximab.

In the literature, three case reports describe vasculitis preceding or occurring early in the course of rheumatoid disease. In one case (2), a 61-year-old man presented with pulmonary vasculitis, with the subsequent development of anti-CCP-positive symmetric polyarthritis as corticosteroid therapy was tapered. In another report (3), a 74-year-old man developed acute cholecystitis within weeks of being diagnosed with RA. Histopathology of the gallbladder after cholecystectomy revealed small vessel vasculitis and rheumatoid nodules. A third case (4) described a 63-year-old male who developed bilateral carpal tunnel syndrome, mononeuritis of both sciatic nerves, and an inflammatory myositis 6 months after being diagnosed with RA. He was treated for presumed RV with prednisolone and intravenous cyclophosphamide but subsequently presented with an acute abdomen and was found to have small bowel perforation at laparotomy. Histopathology revealed medium vessel vasculitis. In all three cases, the patients were positive for anti-CCP antibody and/or RF.

Our present case challenges the long-held view that RV only occurs in patients with long-standing RA and suggests that RV can predate the onset of joint diseases by a considerable time period, particularly if the patient undergoes immunosuppressive treatments.

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