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Editorial Comment

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Refractory rheumatoid vasculitis—a therapeutic dilemma

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The case presented by Kumar *et al*. [1] reminds us of one of the most severe but now rare extra-articular manifestations of rheumatoid arthritis (RA); rheumatoid vasculitis (RV). RV is now a rare condition, with an annual incidence of 3.4/million, and it is now much less common than the anti-neutrophil cytoplasmic antibody (ANCA) vasculitides (AAV) [2]. The incidence has decreased substantially since early methotrexate treatment for RA become common during the 1990s. This reduction has paralleled the general decline in frequency of extra-articular RA, hospital admission rates and need for cervical spine surgery [3–6]. The risk factors for development of RV have long been recognized as male gender, smoking, long standing RA and strong positivity for rheumatoid factor. Recently Makol and colleagues observed in a case control study that the use of hydroxychloroquine and low-dose aspirin reduced the risk of RV [7]. This observation lends support to the idea that because hydroxychloroquine improves lipid profiles that it should be more widely used as a component of combination therapy regimens for RA [8].

The mortality remains high with up to 20% 1-year mortality, again worse than for the AAV [2]. The case highlights the empirical nature of treatment for RV. The traditional approach, which was tried by Kumar *et al*., is intravenous cyclophosphamide following the approach pioneered by Scott and Bacon in the 1980s [9]. Unfortunately, cyclophosphamide failed to halt disease progression and the patient was given intravenous immunoglobulin followed by rituximab. There has been increasing interest in the use of rituximab to treat RV. This approach has been derived from the experience of the use of rituximab in the AAV. Two seminal trials published in 2010 (RAVE and RITUXVAS) showed that rituximab was not inferior to intravenous cyclophosphamide for remission induction especially in relapsing patients [10, 11]. Given that rituximab is effective in uncomplicated RA, it seems logical to extend its use to this situation. In the French Autoimmunity and Rituximab (AIR) registry, there were 17 cases of RV treated with rituximab [12]. Thirteen patients were treated with the conventional RA dose of 1 gm given twice at a 2-week interval, and the remaining four patients received either 0.5 gm or 0.75 g at 2 weeks apart or four infusions of 0.75 g and 1 gm on four occasions at 1-week intervals. Sixteen patients received concomitant glucocorticoids. Remission was achieved in 6 months in 12 patients and 4 had a partial response and 1 had died. At 1 year, 14/17 patients (82%) were in complete remission as defined by a Birmingham Vasculitis Activity Score of 0 combined with an absence of clinical symptoms and signs of disease. Mean prednisolone dosage was reduced from 19.2 to 9.7 mg/day, and at 12 months 14 patients (82%) were in sustained remission. Three patients had severe infections. Whether maintenance therapy required is unknown, the current vogue in AAV is to treat at regular intervals (4–6 months) with of a dose 500–1000 mg for up to 2 years [13, 14]. Again this is a logical approach in RV. The present rarity of RV makes it unlikely that the use of rituximab to treat RV will ever be subjected to a randomized controlled trial.

Modern treatment of RA with treat to target approaches has led to a reduction in this once feared complication of RA, and twenty-first century rheumatologists are now longer confronted with its consequences. But as this case report reminds us RV has not yet completely disappeared and it still carries significant mortality.

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