

Commentary

Clinical and laboratory characteristics of drug-induced vasculitic syndromes

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See related research by Bonaci-Nikolic *et al.* in this issue [<http://arthritis-research.com/content/7/5/R1072>]

Abstract

Clinical recognition of drug-induced vasculitic and lupus-like syndromes is very important because continued use of the offending drug can lead to irreversible and life-threatening vasculitic organ damage (e.g. end-stage renal disease or pulmonary haemorrhage). Withdrawal of the drug often leads to spontaneous recovery, meaning that immunosuppressive therapy can be avoided. The presence of myeloperoxidase-antineutrophil cytoplasmic antibodies, IgM anticardiolipin antibody, and antihistone antibodies in combination was found to be characteristic of drug-induced vasculitic syndromes caused by the antithyroid drugs propylthiouracil and methimazol. Clinically, skin vasculitis and arthralgias predominated and renal vasculitis was rare.

Introduction

The differential diagnosis between drug-induced and idiopathic vasculitic conditions may be difficult in the individual patient. Because the mere withdrawal of the offending drug in the former situation is usually sufficient to attain complete remission of clinical symptoms, the distinction between these syndromes is very important. Failure to recognize a relationship with a drug can lead to fatal organ damage.

The report by Branka Bonaci-Nikolic and coworkers [1] included in this issue of *Arthritis Research and Therapy* is a good example of clinical research aimed at identifying details that can aid in distinguishing between seemingly related syndromes, such as idiopathic vasculitides (IVs) and drug-induced vasculitides (DIVs). The clinical importance of recognizing patients with DIV is great because withdrawal of the offending drug usually leads to resolution of the syndrome without further therapy, whereas the IVs must always be treated with immunosuppressive and anti-inflammatory drugs, and sometimes even with plasmapheresis.

The study included 72 consecutive patients who had been found to be positive for antineutrophil cytoplasmic antibodies

(ANCA) directed at proteinase-3 or myeloperoxidase. Twenty-nine of these patients suffered from Wegener's granulomatosis, 23 from microscopic polyangiitis, four from Churg–Strauss syndrome, and 16 from a DIV caused by either propylthiouracil or methimazol. All sera were additionally studied for presence of antinuclear antibodies (ANAs), antihistone and anticardiolipin antibodies, cryoglobulins, complement factors C3 and C4, C-reactive protein and α_1 -antitrypsin.

Cutaneous vasculitis was found to be most common in the DIV patients, being present in 63%, whereas it was found in only 25% of the IV patients. In contrast, renal vasculitis was seen in 75% of the IV patients but only in 19% of the DIV patients. Four of the DIV patients presented with symptoms compatible with an IV-like syndrome (one Wegener's granulomatosis, three microscopic polyangiitis), whereas 12 patients had a lupus-like syndrome. Thirteen of the 56 IV patients died and eight developed terminal renal failure, whereas there were no deaths and only one terminal renal failure in the DIV group.

Especially interesting findings in this study pertain to the laboratory results. DIV patients were mostly positive for myeloperoxidase-ANCA and were positive for ANAs and antihistone antibodies, and had high levels of IgM anticardiolipin antibodies and low C4 values. This contrasted with absence of ANAs, antihistone and anticardiolipin antibodies, and normal C4 levels in patients with IV.

The study thus concludes that ANCA positive IV patients have a more severe disease course than do patients with DIV. More important, though, is that DIV commonly presents as a lupus-like illness accompanied by serological findings that are distinctly different from those seen in IV. The lower C4 values in the DIV patients indicate complement consumption by immune complexes, and this assumption was supported by the finding of slightly higher cryoglobulin values in these

patients. The fact that DIV patients also harboured high serum levels of IgM anticardiolipin antibodies indicates that DIV patients may be at risk for developing venous or arterial thrombosis or experience pregnancy loss [2]. It may also mean that prophylaxis against such complications should be discussed in DIV patients with the lupus-like syndrome.

There are data in the literature indicating that a lupus-like DIV may develop as a result of antithyroid drug therapy [3]. Authors generally agree that DIV syndromes have a better long-term prognosis mostly because of lesser renal involvement. Arthralgias and skin vasculitis are prominent features in these patients, and the clinical manifestations usually subside after withdrawal of the offending drug. Nevertheless, some patients go on to develop serious vasculitic manifestations if the offending drug therapy is not stopped [4].

Several authors have pointed to the presence of ANCAs directed at more than one neutrophil cytoplasm antigen as a characteristic feature of DIV [4,5]. Others have observed a characteristic development of ANAs and antihistone antibodies as well as myeloperoxidase-ANCAs in such patients, the latter being likely to be caused by drug-induced damage directed at the neutrophils that process the drug [6].

The observation that DIV patients can also develop high levels of IgM anticardiolipin antibodies is partly new. There are very few data in the literature on anticardiolipin antibodies in the IV syndromes, but in cases in which this has been observed the prognosis appeared to be worse because of the development of more extensive lesions.

The development of DIV in conjunction with propylthiouracil or methimazol therapy in patients with Grave's disease is likely to depend on genetic predisposition [7]. Thus, among monozygotic triplets who all developed Grave's disease in their childhood, two were treated with propylthiouracil and one with carbimazol. The two who received propylthiouracil both developed a DIV with skin vasculitis and pronounced arthralgias, whereas the patient who was treated with carbimazol did not.

Conclusion

In conclusion, when a patient manifests prominent skin vasculitis reminiscent of lupus combined with other features of a lupus-like condition, a DIV syndrome should be suspected. Long-term treatment with antithyroid drugs can lead to DIV in genetically predisposed persons, and thus laboratory surveillance follow up is advisable. According to suggestions raised by the report presented in this issue, this should include monitoring of ANCAs, ANAs and anticardiolipin antibodies. Hopefully, this diagnostic approach will lead to better recognition and cure of DIV in the future.

Competing interests

The author(s) declare that they have no competing interests.

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