Netherlands
The Journal of Medicine

REVIEW

Drug-induced vasculitis: a clinical and pathological review

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ABSTRACT

Drug-induced vasculitis is an inflammation of blood vessels caused by the use of various pharmaceutical agents. Vasculitis causes changes in the walls of blood vessels, including thickening, weakening, narrowing and scarring. Inflammation can be short-term (acute) or long-term (chronic) and can be so severe that the tissues and organs supplied by the affected vessels do not get enough blood. The shortage of blood can result in organ and tissue damage, even death. Drug-induced vasculitis is the most common form of vasculitis. The differential diagnosis between drug-induced and idiopathic vasculitic conditions may be difficult in the individual patient. Withdrawal may be helpful to distinguish between these syndromes. Withdrawal of the offending agent alone is often sufficient to induce prompt resolution of clinical manifestations, obviating the need for immunosuppressive and anti-inflammatory drugs. Increasing understanding of the pathophysiological characteristics of all inflammatory vasculitides should lead to better diagnostic and therapeutic approaches to drug-induced vasculitis.

KEYWORDS

Vasculitis, drug induced vasculitis, antineutrophil cytoplasmic antibodies (ANCA)

INTRODUCTION

This review aims to draw attention to the features that distinguish drug-induced vasculitis from those of idiopathic autoimmune syndromes, first and foremost primary vasculitides. A systemic drug-induced syndrome only develops in a minority of patients treated with a drug over a prolonged period of time, whereas cutaneous vasculitis occurs quite commonly.[1,2] The most frequent symptoms at onset are arthralgia, myalgia and skin rash. Early withdrawal of the offending drug usually leads to complete recovery while more advanced disease and late withdrawal of the drug may necessitate use of immunosuppressive therapy. The recent discovery of anti-neutrophil cytoplasm antibodies (ANCA) directed to myeloperoxidase (MPO) in a large serological subset of drug-induced vasculitis caused by long-term anti-thyroid drug treatment has opened new avenues for differential diagnostics.[2,3] Certain medications such as propylthiouracil can induce ANCA-associated vasculitis. This review focuses on the data on causal drugs, possible pathogenesis, clinical description, diagnosis, treatment and prognosis of patients with drug-induced vasculitis. ANCA with specificity to more than one lysosomal antigen combined with the presence of antibodies to histones and beta-2 glycoprotein 1 constitutes a unique serological profile for drug-induced vasculitis.[4]

The pathogenesis of drug-induced ANCA-associated vasculitis might be multifactorial. The clinical manifestations are similar to those of primary ANCA-associated vasculitis, but ANCA with multi-antigenicity may help to differentiate it from primary ANCA-associated vasculitis.[5] Rational use of laboratory marker profiles is likely to aid in distinguishing drug-induced from idiopathic syndromes. However, the use of ANCA and other autoantibodies as biomarkers of different phenotypes of drug-induced vasculitis is one of the focuses of this review.

Evidence is mounting that these specific antibodies are pathogenic in small-vessel vasculitis.[6,7] However, the aetiology of ANCA-associated vasculitis is largely unknown.

The diagnosis of drug-induced ANCA-associated vasculitis is based on the temporal relationship between clinically evident vasculitis and administration of the offending drugs, and excluding medical conditions that mimic

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vasculitis and other definable types of vasculitis.[8] After the diagnosis of drug-induced ANCA-associated vasculitis is made, the offending drugs should be withdrawn immediately, and appropriate immunosuppressive therapy should only be administered to patients with vital organ involvement. The duration of immunosuppressive therapy should be much shorter than that in primary ANCA-associated vasculitis and long-term maintenance therapy might not be necessary. The prognosis of patients with drug-induced ANCA-associated vasculitis is good as long as the offending drug is discontinued in time.

Table 1. *Medications associated with drug-induced vasculitis*

Antibiotics
Cephotaxime
Minocycline
Anti-thyroid drugs
Benzylthiouracil
Carbimazole
Methimazole
Prophythiouracil
Anti-tumour necrosis factor-α agents
Adalimumab
Etanercept
Infliximab
Psychoactive agents
Clozapine
Thioridazine
Miscellaneous drugs
Allopurinol
D-Penicillamine
Hydralazine
Levamisole
Phenytoin
Sulfasalazine

GENERAL FEATURES

Drug-induced vasculitis usually attacks the skin and sometimes the subcutaneous part of the skin, but sometimes also the kidneys and the lungs.[9,10] Clinical symptoms include arthralgias and myalgias but usually do not develop into overt arthritis or myositis, manifested as muscle weakness. End-stage kidney disease due to glomerular vasculitis may occur, but early removal of the offending drug usually leads to resolution of the glomerular inflammation. A few cases of drug-induced vasculitis presenting with a haemorrhagic syndrome due to lung capillaritis have been reported. Patients with drug-induced vasculitis typically harbour ANCA directed to one or more neutrophil cytoplasm antigens, the most common antigens being the granule proteins MPO, HLE, cathepsin G, and lactoferrin.[11-14] In one study the levels of MPO-ANCA were found to be much higher in 30 patients with drug-induced MPO-ANCA vasculitis than those usually found in idiopathic vasculitides, and there was a strong association between presence of HLE-ANCA and lactoferrin-ANCA and exposure to the candidate drugs.[15] Other research showed a strong association between heredity and development of drug-induced vasculitis during treatment with propylthiouracil in monozygotic triplets with Graves' disease.[16] Two of these children, who were treated with propylthiouracil, had multispecific ANCA including HLE-ANCA, while the third triplet had no signs of drug-induced vasculitis and no ANCA during treatment with carbimazole.

To date, many studies have indicated that drug-induced vasculitis may be a complication of therapy with prior use of certain medications in some patients, and unreported and/or undiagnosed cases may be beyond our imagination. As shown in *table 1*, the most often implicated drug in the published work is propylthiouracil, which may result from more frequent prescriptions in clinical practice.[13,17,18] Propylthiouracil is a common anti-thyroid drug widely used all over the world. In the published work, over 100 cases of propylthiouracil-induced vasculitis have been reported. Further studies in pathogenesis, treatment and long-term outcomes of patients with propylthiouracil-induced vasculitis provide useful information on understanding drug-induced vasculitis.[19] It has been shown that propylthiouracil is implicated in 80 to 90% cases of vasculitis induced by anti-thyroid drugs, while cases related to other drugs, such as methimazole, carbimazole and benzylthiouracil, are less frequent.[20] Clear evidence for an association with the development of drug-induced vasculitis has also been shown for the following drugs: hydralazine, anti-tumour necrosis factor-α (TNF-α) agents, sulfasalazine, D-penicillamine and minocycline; however, most of this evidence was limited to case reports.[21-25] The increasing use of so-called 'biological' agents in medical practice has been accompanied by growing evidence on the toxicity profile of these agents, including drug-induced vasculitis. Anti-TNF-α drugs, such as adalimumab, infliximab and etanercept, are now established therapy in the management of rheumatoid arthritis and several other chronic inflammatory diseases. Repeated treatment with these agents can lead to the development of autoantibodies, including antinuclear antibodies (ANA), anti-dsDNA and anti-cardiolipin antibodies, in up to 10% of patients.[26] The autoantibody synthesis is associated with a greater cumulative dose of therapy. Although uncommon, some patients receiving anti-TNF-α agents were found to develop vasculitis.[22] Medications, such as biological agents, are geared toward targeting specific immune mechanisms, and they may skew the immune response dramatically.

Leukotriene antagonists (LTA, such as montelukast and zafirlukast) have been implicated in the pathogenesis of

Churg-Strauss syndrome (CSS). Further studies showed that no significant association was observed between CSS and LTA after controlling for the use of other anti-asthma drugs.[27] In a case-crossover study, it was suggested that the onset of CSS might not be associated with montelukast but a phenomenon possibly associated with a group of medications prescribed for long-term control of severe asthma.[28] Based on this evidence, the National Institutes of Health/USA Food and Drug Administration panel concluded that no one class of LTA was associated with CSS and that LTA are safe.[29] Our study group described two patients treated for a few years before they developed symptoms of CSS.[30]

PATHOGENESIS

The pathogenesis of drug-induced vasculitis is unclear. A variety of agents may produce a typical clinical picture together with a similar autoimmune profile, suggesting a common mechanism for drug-induced vasculitis. To date, the mechanism is far from fully understood and it might be multifactorial. Most drugs are low-molecular-weight substances, and require the formation of a complex to stimulate antibody formation and then to drive an immune response.[31] One hypothesis proposed that activated neutrophils in the presence of hydrogen peroxidase released MPO from their granules, which converted the offending drugs such as prophythiouracil and hydralazine into cytotoxic products; then the drugs and their metabolites were immunogenic for T cells, which in turn activated B cells to produce ANCA.[32] The offending drugs and their metabolites may accumulate within neutrophils, bind to MPO and modify its configuration, with subsequent intermolecular determinant spreading the autoimmune response to other autoantigens and turning neutrophil proteins (including elastase, lactoferrin and nuclear antigens) immunogenic.[3] Some drugs such as sulfasalazine could induce neutrophil apoptosis.[23] Moreover, neutrophil apoptosis, in the absence of priming, is associated with translocation of ANCA antigens to the cell surface, which then induce the production of ANCA, and ANCA in turn are able to bind the membrane-bound antigens, causing a self-perpetuating constitutive activation by cross-linking PR3 or MPO and Fcγ receptors.[33]

CLINICAL MANIFESTATIONS

The clinical manifestations of drug-induced vasculitis are similar to those of primary vasculitides, which range from less specific syndromes (fever, malaise, arthralgia, myalgia, weight loss) to single tissue or organ involvement and life-threatening vasculitis.[34] Some researchers suggested that more severe specific organ involvement might develop in patients with non-specific systemic syndrome when the causal drug was not withdrawn in time.[35] The kidney is the most commonly involved organ and the renal features vary widely, including haematuria, proteinuria and elevated serum creatinine.[36] Intra-alveolar haemorrhage is the most commonly reported pulmonary manifestation with consequent cough, dyspnoea and haemoptysis.[37] Some patients may only have lung involvement such as acute respiratory distress syndrome and interstitial pneumonia and without renal injury.[38] Contrary to idiopathic vasculitides, drug-induced vasculitis usually has a milder course, and fewer patients have rapidly progressive glomerulonephritis in drug-induced vasculitis.[39] Rare clinical manifestations were also described in case reports such as sensorineural hearing loss, pericarditis, pyoderma gangrenosum, central nervous system vasculitis presenting as cognitive symptoms and cerebral pachyleptomeningitis.[40-46]

There is no unique clinical pathological or laboratory marker for discrimination between drug-induced vasculitis and other vasculitides.[8] A low percentage of patients treated long term with a drug risk develop hypersensitivity reactions, some of which appear as vasculitis. There are laboratory markers that can help distinguish drug-induced vasculitis from idiopathic autoimmune diseases, and thorough knowledge about such serological changes may help to differentiate drug-induced from idiopathic syndromes (summarised in *table 2*).

The laboratory abnormalities could indicate organ involvement. Anaemia is common in patients with drug-induced vasculitis.[34] Urine abnormalities have consisted of haematuria and proteinuria in patients with kidney vasculitis.[34] Accurate assessment of disease activity within the lungs may be difficult because disease activity correlates poorly with pulmonary symptoms. A plain chest radiograph is a tool to monitor disease activity and high-resolution computed tomography (CT) scanning of the chest offers a more sensitive imaging technique.[38]

Table 2. *Laboratory marker differences between drug-induced vasculitis and idiopathic systemic lupus erythematosus and ANCA-associated vasculitis*

	Drug-induced vasculitis	SLE	AAV
Antihistone abs.	Can be seen	Rare	Absent
AntidsDNA abs.	Absent	Common	Absent
ANCA	Common[a]	Rare	Common[b]
Antiphospholipid abs.	Common	Common	Rare
Immune complexes	Rare	Common	Absent

SLE = systemic lupus erythematosus; AAV = anti-neutrophil cytoplasmic antibody-associated vasculitis, abs. = antibodies; [a] Multispecific; [b] Single ANCA specificity.

Although acute-phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) are usually elevated in patients with drug-induced vasculitis on diagnosis, they are neither sufficiently sensitive nor specific in making the diagnosis.[4]

Because detection of ANCA might serve as a warning of the possibility of drug-induced vasculitis, ANCA assays using combined IIF and antigen-specific enzyme-linked immunosorbent assays (ELISA) rather than relying on either test alone are recommended in all patients suspected of drug-induced vasculitis.[47] Tissue biopsy is usually necessary to provide a definitive diagnosis of vasculitis and to exclude other diseases. Specimens may come from skin lesions, renal and lung biopsies.[34]

However, the diagnosis of drug-induced vasculitis is complicated and difficult for several reasons, including: (a) physicians often do not recognise the syndrome as drug-induced (inappropriate diagnosis); (b) variable and often prolonged duration between the commencement of therapy and initial vasculitic symptoms; and (c) failure to evaluate appropriate laboratory and invasive tests. The awareness of drug-induced vasculitis by physicians is important in order to make a prompt diagnosis and start treatment and thus achieve a favourable outcome. It is essential that a comprehensive drug history is obtained in patients with vasculitis. Clinicians should seek information on drug use for at least six months before presentation. The evaluation of pertinent laboratory data and prompt histological confirmation of the disease may aid in the diagnosis. Biopsies are strongly encouraged to confirm the presence of vasculitis and to determine the disease severity.[47] We suggest that drug-induced vasculitis should be defined further by the following: (a) the signs and symptoms of vasculitis are temporally related to using the offending drug, and regressed with its discontinuation; (b) serum ANCA is positive, especially those with multi-antigenicity; and (c) medical conditions that mimic vasculitis are excluded, especially infections and malignancies, and other definable types of vasculitis.[47]

Table 3. *Treatment strategy for patients with drug-induced vasculitis*

Management of causal agents	
Withdrawal	
Avoid re-challenges	
Consider avoiding similar drug classes	
Individualised therapy	
Non-specific symptoms	Withdrawal of causal agents alone
Organ involvement	Corticosteroid and/or immunosuppressive drugs
Severe organ involvement (e.g. necrotising GN, focal segmental necrotising GN, diffuse alveolar haemorrhage)	Methylprednisolone pulse therapy, followed by combined corticosteroid and immunosuppressive drugs
Massive pulmonary haemorrhage	Plasmapheresis
Special notes for patients with drug-induced vasculitis	
A shorter course of immunosuppressive therapy	
Long-term maintenance may not be necessary	
Monitoring of serum ANCA Surveillance for emergence of a chronic underlying vasculitis	

ANCA = anti-neutrophil cytoplasmic antibodies; GN = glomerulonephritis.

TREATMENT

There is no standard approach to the treatment of drug-induced vasculitis (summarised in *table 3*). Because the pathogenesis is different between primary and drug-induced vasculitis, the cornerstone of treatment for primary ANCA-associated vasculitis, including induction therapy and maintenance therapy with combined corticosteroid and cyclophosphamide, might not be suitable for patients with drug-induced vasculitis. Treatment should be based on individualised assessment in patients with drug-induced vasculitis. Therefore, treatment for patients with organ involvement should depend on the severity of clinical manifestations and histopathological lesions. In drug-induced vasculitis, the first step is the discontinuation of the medication. For patients with severe and active organ involvement, intensive immunosuppressive therapy could improve organ function and prevent progression to severe, irreversible disease. As shown in *table 2*, prednisone should be administered at 1 mg/kg per day for the first four to eight weeks, followed by a gradual tapering within six to 12 months.[48] In the setting of respiratory failure, alveolar haemorrhage and progressive renal failure, therapy should include cyclophosphamide and high-dose corticosteroids. Intravenous methylprednisolone in doses of 1000 mg/day for three days may be considered.[48] Different approaches have been described. In the first one, cyclophosphamide is administered in monthly boluses for six months, then every three months for two years. The alternative is to give the monthly boluses for six months, and then use azathioprine daily for two years.[48] In addition, patients with life-threatening massive pulmonary haemorrhage may respond to plasmapheresis.[49] Mycophenolate mofetil is an alternative in the treatment of severe drug-induced vasculitis.[48] It is an immunosuppressive agent: inosine monophosphate dehydrogenase 23 inhibitor.[50] It is well accepted that treatment for patients with primary ANCA-associated vasculitis comprises both induction and maintenance therapy. However, for patients with drug-induced vasculitis, the duration of immunosuppressive therapy is still inconclusive. The duration of

immunosuppressive therapy in patients with drug-induced vasculitis could be much shorter than that in primary ANCA-associated vasculitis, and that as long as the offending drug was withdrawn, maintenance therapy might not be necessary.[48] Although ANCA detection may provide a clue to the diagnosis of drug-induced vasculitis, positive seroconversion alone may not be a sufficient reason to discontinue the offending drug, because only a small proportion of the patients with positive ANCA will actually develop clinically evident vasculitis.[47] Physicians should carefully monitor those with drug-induced ANCA but without clinical vasculitis. Resolution of most symptoms has generally occurred within one to four weeks except for severe organ involvement.[8] Nonspecific symptoms may resolve dramatically only after cessation of the causal drug. Although complete resolution of vasculitis occurred in most of the reported cases, some patients do have persistent laboratory abnormalities (elevated serum creatinine, proteinuria) throughout a long-term follow-up. As we mentioned before, if necrotising crescentic glomerulonephritis was present, the patients were at high risk of developing chronic renal failure.[39]

CONCLUSION

There are no clear data on the prevalence of drug-induced vasculitis due to lack of prospective studies. Several cross-sectional studies reported that the prevalence of propylthiouracil-induced vasculitis ranged from 20% to 64%.[51] Prospective, longitudinal studies with a larger cohort of patients are needed to establish the true prevalence of drug-induced vasculitis. The clinician needs to be aware of this risk and quickly stop the offending drug therapy if signs of drug-induced vasculitis develop. In conclusion, patients undergoing treatments with the drugs able to induce vasculitis should be monitored closely during long-term therapy. ANCA is a useful tool to diagnose vasculitis. Appropriate immunosuppressive therapy should only be administered to patients with vital organ involvement in order to prevent progression to severe, irreversible disease. The duration of immunosuppressive therapy should be much shorter than that of primary ANCA-associated vasculitis and long-term maintenance therapy might not be necessary.[48] Identification of predisposing factors to drug-induced vaculitis may provide insight into the pathogenesis of primary vasculitis. Finally the recommendations for clinicians are:

- Avoid use of the drugs able to induce vasculitis in the long term, and patients on long-term treatment with these drugs should be monitored carefully.
- Discontinue the offending drug immediately upon diagnosis of drug-induced vasculitis.
- Individualised immunosuppressive therapy should be initiated according to the severity of organ involvement.
- Adequate documentation of the potentially serious drug-induced reaction in patients' medical records is necessary to avoid re-challenge.

As new classes of medications for the treatment of many disorders are developed, we expect that the number of agents causing drug-induced vasculitis will increase, especially in the era of targeted immune modulation. Drug-induced vasculitis and the unexpected effects of these newer medications continue to be described, demonstrating our present limited understanding of the immune system, and our inability to predict the consequences of manipulating its complex homeostatic mechanisms.

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