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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Drug-Induced Vasculitis: New Insights and a Changing Lineup of Suspects

Rafael G. Grau[1]

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Abstract An increasing number of therapeutic agents have been associated with a vasculitic syndrome. This usually involves small vessels, primarily capillaries, venules, and arterioles in leukocytoclastic vasculitis, small-vessel disease similar to an antineutrophil cytoplasmic antibody-related vasculitis, or mid-sized muscular arteries in a polyarteritis-like picture. Antineutrophil cytoplasmic antibodies are present in many cases of vasculitis regardless of the size of the vessel involved. Monoclonal antibodies used to treat many autoimmune disorders have become the most common agents associated with drug-induced vasculitis. Important advances in epigenetics, genetics, and neutrophil apoptosis are providing new insights into the pathogenesis of both drug-induced vasculitis and idiopathic vasculitis. Although management has not changed significantly in the past few years where withdrawal of the offending agent is the primary intervention, increasing awareness of drug-induced vasculitis can lead to earlier diagnosis and prevention of severe organ damage and fatalities.

Keywords Antineutrophil cytoplasmic antibodies · Cocaine · Drug-induced vasculitis · Hydralazine · Leukotrienes antagonists · Levamisole · Minocycline · Monoclonal antibodies · Propylthiouracil · Rituximab · Statins · Tumor necrosis factor-alpha · Vasculitis

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✉ Rafael G. Grau
rgrau@email.arizona.edu

[1] Division of Rheumatology, University of Arizona College of Medicine, 1501 N. Campbell Ave #8303, Tucson, AZ 85724, USA

Introduction

Vaculitis is a heterogeneous group of diseases with many etiologies including autoimmune diseases, infections, and medications. Among the small- and medium-sized vessels, the recognition of the subset of drug-induced vasculitis (DIV) is important because the treatment strategy and prognosis are different from that of the idiopathic forms. PA Merkel has defined drug-induced vasculitis as "any case of inflammatory vasculitis in which a specific drug (including toxins) is established as a causal agent of disease when other forms of vasculitis are excluded" [1]. The 2012 International Chapel Hill Consensus Conference (2012 CHCC) on nomenclature has incorporated definitions for DIV based on the advances in our understanding of these conditions, increasing the awareness and importance to this subset of vasculitis [2••]. In addition, new insights into the pathogenesis of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis have been derived from human and animal models of DIV as well as from parallel fields of genetics and epigenetics.

In broad terms, the clinical presentation of DIV can be nonspecific with arthralgias, myalgias, and skin rash [3]. While small-vessel vasculitis is the most commonly reported form of drug-induced vasculitis, it represents only 10–20 % of cutaneous reactions to drugs [4] so a skin biopsy is almost always desirable. On occasion, organ involvement occurs including the lung, kidneys, central nervous system, and liver with clinical features of an idiopathic ANCA-related disease or a polyarteritis nodosa (PAN)-like vasculitis. Distinguishing a drug-related ANCA-positive disease or a PAN-like disease from the idiopathic counterparts is difficult and requires a high level of suspicion. It has been proposed that the simultaneous presence of mutiple ANCA specificities in conjunction with antinuclear antibodies (ANA), antibodies to histones or B_2 glycoprotein-1 is strongly suggestive of a diagnosis of DIV

[5]. Withdrawal of the offending agent is frequently all that is necessary for treatment, but severe disease will require glucocorticoids and immunosuppressive agents.

This review will concentrate on the literature of the last 5 years that broadens our understanding of DIV. More thorough and systematic reviews of medications associated with vasculitis are available elsewhere [4, 6].

Categorization of the Vasculitides

Attempts at defining and classifying the vasculitides have been an ongoing effort since the 1950s. The vasculitides are an uncommon, heterogeneous group of diseases that share the pathological hallmark of blood vessel inflammation. This translates into a great variety of clinical presentations. The American College of Rheumatology (ACR) proposed a classification criteria in 1990 to discriminate among patients with vasculitis. The experts identified seven forms of vasculitis: polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, hypersensivity vasculitis, Henoch-Schonlein purpura, giant cell (temporal) arteritis and Takayasu arteritis [7]. Many forms of vasculitis, particularly microscopic polyangiitis (MPA), were not recognized at that time. The next significant step occurred in 1994 with the Chapel Hill Consensus Conference (1994 CHCC) on nomenclature defining ten vasculitic syndromes and distinguishing MPA from PAN [8]. The 2012 CHCC on nomenclature utilized the advances in vascular research made over the past decade to add categories of vasculitis and update names and definitions using etiological, pathogenetic, clinical, and pathologic characteristics (Table 1). These definitions are however, only the first step in developing classification and diagnostic criteria and should not be used as either [2••]. An ACR/EULAR-endorsed study to develop these criteria is underway.

Among the changes made by the 2012 CHCC on nomenclature and categorization was the addition of a new category of "Vasculitis associated with probable etiology." This includes two forms of drug-associated vasculitis: one is an immune complex variant and the other is an ANCA-associated form. It is recommended that a vasculitis associated with a probable specific etiology should have the name of the agent as a prefix specifying the association (e.g., hydralazine-associated microscopic angiitis, cancer-associated vasculitis, etc.) [2••]. An important caveat is that not all patients with clinical and histopathology features consistent with ANCA-associated vasculitis (AAV) test positive for ANCA [9] and this may be true in DIV as well.

Table 1 Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides [2••]

- Large vessel vasculitis (LVV)
  - Takayasu arteritis (TAK)
  - Giant cell arteritis (GCA)
- Medium vessel vasculitis (MVV)
  - Polarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- Small-vessel vasculitis (SVV)
  - Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
    - Microscopic polyangiitis (MPA)
    - Granulomatosis with polyangiitis (Wegener's) (GPA)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
    - Antiglomerular base membrane (anti-GBM) disease
    - Cryoglobulinemic vasculitis (CV)
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (antiC1q vasculitis)
- Variable vessel vasculitis (VVV)
  - Behçet disease (BD)
  - Cogan's syndrome (CS)
- Single-organ vasculitis (SOV)
  - Cutaneous leukocyte angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- Vasculitis associated with systemic disease
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- Vasculitis associated with probable etiology
  - Hepatitis C virus-associated cryoglobulinemic vasculitis
  - Hepatitis B virus-associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Pathogenesis

The pathogenesis of drug-induced vasculitis is poorly understood. It appears to be multifactorial and requires an environmental trigger leading to self-reactivity in an individual with genetic predisposition. Certain drugs, sometimes associated with lengthy exposures, can induce clinical signs that are typically found in idiopathic vasculitic diseases. It can be preceded by abnormal serologies (i.e., ANCA) without clinically apparent disease. The key difference between DIV and

idiopathic vasculitis is that in the overwhelming majority, cessation of drug therapy seems to correct the autoimmune state [10•]. This outcome above all distinguishes the DIV from the idiopathic forms of vasculitis.

A variety of agents may produce similar clinical pictures suggesting a common pathway for DIV [11]. Most drugs are low molecular weight substances that have been thought to require attachment to a macromolecule or modification to lead to antibody production [4]. Released myeloperoxidase (MPO) from activated neutrophils can convert propylthiouracil (PTU) and hydralazine into immunogenic metabolites that induce the production of ANCA [12]. Some drugs like sulfasalazine can provoke neutrophil apoptosis leading to movement of ANCA antigens to the cell surface and production of ANCA [13]. Neutrophil apoptosis in the absence of priming can lead to translocation of ANCA antigens to cell membrane, which can induce the production of antibodies. Binding of these antibodies to the cell membrane may further activate the neutrophils [14].

While this fragmentary information is of interest, it has been the recent advances in our understanding of all AAV that are providing promising insights into the pathogenesis of DIV. Important discoveries in the last decade have helped bring attention to new environmentally-related factors (epigenetics), the genetic predisposition, and a new form of cell death called NETosis, which provides unique exposure of enzymes to the immune system.

Epigenetics

Epigenetics is defined as heritable changes in gene expression that do not involve alterations in gene sequence. Epigenetic mechanisms are important in controlling patterns of gene expression. They are sensitive to environmental control such as UV light exposure, diet, and lifestyle [15]. The primary mechanisms of epigenetic gene regulation includes methylation and histone modification. These interact with each other in modulating chromatic architecture in turn allowing gene transcription or repression [16]. Hydralazine affects DNA methyltransferase (DNMT) inhibiting the extracellular signal-regulated kinase (ERK) pathway similarly seen in idiopathic lupus [17]. Levels of the histone H3K27me3 associated with gene silencing of proteinase 3 (PR3) and MPO are perturbed in patients with AAV leading to aberrant expression. At the same time, a demethylase called Jumonji Domain Containing 3 (JMJD3) for this histone is increased in hydralazine-induced AAV as compared to healthy persons. Further elaboration of this complex process is beyond the scope of this review [18]. Another mechanism possessed by hydralazine is to reverse epigenetic silencing of tumor suppressor in cancer cells [19], and reversal of epigenetic silencing could occur with PR3 and MPO [20•].

MicroRNAs, a class of noncoding ribonucleic acids (RNAs), play key roles in the regulation of genetic expression as well. Certain microRNAs are aberrantly expressed in SLE [21]. MicroRNA 18 1b is a potent regulator of downstream of NF-kappa signaling and leukocyte influx in vascular endothelium. The rescue of this microRNA in endotoxemic mice led to decreased NF-kappa signaling and diminished lung injury and mortality [22•]. Their role in the vasculitides is still unknown.

Genetics

For several chronic inflammatory diseases, the finding of a familial aggregation has suggested a role for genetic factors. Familial aggregation of granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis (WG) demonstrates a relative risk of 1.56 for first-degree relatives as compared to control subjects [23]. Another study revealed a strong association of GPA with an allele encoding class II molecule DPBI*0401 with an odds ratio of 3.91 [24]. An association has been suggested between AAV and the rare Z (or null) allele of the serpin A1 gene (SERPINA1) that encodes alpha-1 antitrypsin, a serine proteinase inhibitor for which PR3 is one of the several substrates [25, 26].

A genome-wide association study was performed to investigate the genetic base for two major forms of ANCA-associated vasculitis, GPA and MPA. It was found that both major histocompatibility complex (MHC) and non-MHC associations for GPA and MPA were genetically distinct. The strongest associations were for the genetic specificity of ANCA and not the clinical syndrome. PR3-ANCA was associated with HLA-DP and the genes encoding alpha-1 antitrypsin (SERPINA1) and PR3 (PRTN3). MPO-ANCA was associated with HLA-DQ [27]. These studies confirm that there is a genetic component to AAV.

Neutrophil Extracellular Traps

A novel and relevant form of cell death in which the apoptotic granulocyte releases nuclear chromatin has been described. It is referred to as neutrophil extracellular traps (NETs) and may serve to immobilize infectious microbes. The production of NETs that results from cell death is called NETosis [28, 29]. ANCA-induced NETs in vitro were found in kidney biopsy specimens from patients with idiopathic small-vessel vasculitis [30].

Using PTU to inhibit the full release of NET chromatin, Nakazawa et al. found that the altered morphology of PTU-induced NETs correlated with an increased resistance to nucleolytic degradation, thereby prolonging the exposure of MPO to the immune system perhaps facilitating the appearance of MPO-ANCA [31••]. This is very relevant, as it has been demonstrated that antibodies to MPO are directly

involved in the pathogenesis of vasculitis manifested by crescentic glomerulonephritis and pulmonary hemorrhage in mice. These manifestations could be transferred from immunized animals to naive animals by transfer of purified anti-MPO IgG [32]. Neutrophils play a critical role as their absence leads to reduced severity of symptoms in mice [33]. Incubation of neutrophils with ANCA leads to degranulation and reactive oxygen production [34]. In addition to its contribution to MPO-ANCA in PTU-induced vasculitis, NETosis may be a relevant source of other autoantigens in autoimmunity [10•].

Therapeutic Agents

A literature search was conducted in March 2015 and updated in June 2015. Several databases were searched including PubMed, Embase, Scopus, and Web of Science. The search result included all publications in the English language and was not limited to any time span. Search terms included "drug-induced vasculitis" as a text word, and controlled vocabulary when available.

The agents most frequently reported in our search of the literature in the past 5 years are in the following order of frequency: (1) tumor necrosis factor (TNF) inhibitors, (2) propylthiouracil, (3) cocaine/levamisole, (4) hydralazine, (5) minocycline, (6) rituximab, (7) montelukast, and (8) statins. The number of publications rather than the actual number of cases was used to create this list as the number of cases varied greatly from publication to publication. These articles reflect the areas of interest at the time of their publication and may not reflect the most common casative agents occurring in clinical practice. As the number of publications per therapeutic agent was low, a noticeable variation from year to year was noted. It is clear however that the biological agents utilized in rheumatic patients including TNF inhibitors, rituximab, and other monoclonal antibodies have been increasingly implicated in DIV. Newer biological agents appear for the first time such as the TNF inhibitor, i.e., golimumab [35, 36], and non-TNF inhibitors such as tocilizumab [37] and abatacept [38].

The clinical presentation is quite varied and ranges from nonspecific fever, arthralgias, myalgias, and rash to single or multiple organ involvement. The latter may be very similar to primary or idiopathic vasculitis. The kidney is the most commonly involved organ with hematuria, proteinuria, and a rise in serum creatinine. Pulmonary manifestations include cough, dyspnea, and hemoptysis representing alveolar hemorrhage. Rare cases of liver, peripheral, and central nervous system involvement are described. Early recognition of a drug-induced vasculitis is important, as it appears that longer duration of drug exposure is associated with more severe manifestations. There is no unique clinical, laboratory, or pathologic finding so a high index of suspicion is necessary.

Tissue Necrosis Factor Inhibitors

Biological agents, particularly TNF inhibitors, continue to grow in use for the management of a wide array of rheumatic and immunologic diseases. Paradoxically, they are also the cause of autoimmune diseases such as cutaneous vasculitis, lupus-like syndrome, systemic lupus erythematosus, and interstitial lung disease. By 2012, TNF inhibitors have become the leading group of reported cases of DIV. There are over 200 cases reported worldwide [39•].

A single-center report of eight cases related to TNF inhibitors from the USA stated that the time between initiation of treatment and the onset of vasculitis of treatment duration was between 2 and 72 months with a mean of 34.5 months [39•]. The characteristics are similar to what has been reported in other DIVs with a female preponderance and a mean age of 48.5 years. Cutaneous manifestations were most common (63 %) with palpable purpura as the most common variant of skin disease. Other cutaneous manifestations included ulceration, blisters, and erythematous macules. Systemic vasculitis was seen in the same percentage (63 %) with renal and peripheral neuropathy as the most common noncutaneous involvement. All five skin biopsies performed showed leukocytoclastic vasculitis (LCV) and two of the three nerve biopsies showed perivascular epineural inflammation and the third revealed perivascular inflammation and increased rate of axonal degeneration. The kidney biopsy demonstrated a mild IgA nephropathy [39•]. Two other series, one French and another Spanish, show similar overall findings [40, 41].

As in most DIV, discontinuation of the offending agent is the key management step to be taken. Mean time to at least partial resolution was 6.9 months. No recurrence of vasculitis was noted [39•]. Rechallenging with the same drug is a rare event, and relapse of the vasculitis occurred in six of nine patients (67 %) when it was the same TNF inhibitor [42] and 33 % when another TNF inhibitor was used [41]. The development of antibodies to ANA and anti-dsDNA is well recognized in DIV including TNF inhibitors. Percentages between 25 and 80 % for ANAs and between 5 and 15 % for anti-dsDNA antibodies have been reported in patients receiving TNF inhibitors [43].

Propylthiouracil

PTU, carbimazole, and methimazole are thionamide compounds commonly used in the treatment of Graves's disease and other forms of hyperthyroidism. Reports of DIV appeared in the 1970s but it is a rare event occurring in 1/10,000 patients. Asymptomatic serum ANCA positivity occurs in 32–41 % of PTU-treated patients with a median onset of 42 months [44, 45]. Adverse events described have included agranulocytosis, hepatitis, interstitial pneumonitis, rheumatic manifestations, serum sickness-like illness, PTU-induced

lupus, and vasculitis [3]. The initial symptoms are nonspecific with fever, fatigue, weight loss, and arthralgias. Prolonged exposure may lead to serious and sometimes fatal complications including alveolar hemorrhage [46] and renal failure [47]. Other less commonly reported manifestations include oropharyngeal involvement in the form of necrotizing oral ulcers [48], purpuric rash of the auricular pinnae [49], erythema nodosum, pyoderma gangrenosum [50], and bone marrow plasmocytosis with granulocytopenia mimicking a plasma cell dyscrasia [51].

Serological studies reveal a high-titer MPO-ANCA with a perinuclear ANCA pattern on indirect immunofluorescent technique (IFT). Occasionally, the autoantibody is directed to PR3-ANCA but multiantigenicity with other cytoplasmic enzymes including lysozyme, lactoferrin, elastase, and bactericidal permeability increasing protein can be seen [52]. A comparison of PTU-ANCA vasculitis with primary ANCA vasculitis in a Chinese population revealed a predilection for younger persons and females with less hypertension, and milder renal diseases were noted in the PTU-ANCA vasculitis group [53]. A switch from PTU to methimazole is usually successful with resolution of the DIV, but occasional relapses occur with the methimazole [54]. Discontinuation of the antithyroid medication leads to resolution of the vasculitis. In a follow-up of 15 patients, no relapses occurred within a mean follow-up of 55 months. Twelve patients had complete resolution, and one had partial resolution. Two patients treated at an advanced stage of disease were resistant to treatment and developed end-stage renal disease [55].

Levamisole/Cocaine

In 2008, reports of cocaine and crack cocaine users developing agranulocytosis and purpuric skin lesions surfaced. The distribution of the skin involvement was in the extremities, the nose, cheeks, and ears. Biopsy revealed a thrombotic vasculitis with a variable neutrophilic infiltrate similar to LCV [56]. Previous experience with levamisole as an immune modulator for rheumatoid arthritis, pediatric nephrotic syndrome, and breast cancer in the late 1970s suggested that this agent was the cause of the clinical manifestations seen in cocaine abusers [57•]. The use of levamisole to "cut" cocaine started in 2002 and, by 2009, was in 69 % of seized cocaine [58].

The clinical picture can be nonspecific with fever, arthralgias, and myalgias and can be followed by purpuric skin involvement noted before and on occasions, with hemorrhagic bullae in the lower extremities [59]. Cocaine itself is associated with multiple organ involvement including the skin, the lungs and the cardiovascular, renal, and nervous systems so prompt urine testing can demonstrate the presence or absence of levamisole [60]. In addition to the neutropenia, a positive ANCA with one or several antigenic specificities can be seen. Elevated levels of antibodies to human neutrophilic elastase have been associated with cocaine-related disease [61]. Other antibodies such as ANA and antiphospholipid antibodies can be present. Immunohistochemical and immunofluorescence studies of cocaine-associated retiform purpura have shown a very striking thrombotic diathesis with intravascular macrophage accumulation, prominent intracellular expression of ICAM-1/CD54, and extensive vascular deposition of C5b-C9. Murine models show that these events occur prior to the appearance of ANCA or antiphospholipid antibodies [62].

A subset of patients who insufflate (sniff) cocaine develop severe damage to the upper airways with perforation of the hard palate called inflammatory cocaine-induced midline destructive lesions (CIMDLs). Patients who develop this lesion have positive ANCA as opposed to comparable users who do not have this destruction. It is speculated that the subset of patients who are capable of producing the elastase-ANCA may have a more severe necrotizing inflammatory tissue response [63•].

A patient who developed weakness, rash, and myalgia after a 5-day course of levamisole for recalcitrant warts turned out to have a CPK elevation of 1026 IU/L and EMG changes compatible with an inflammatory myopathy and a rash that showed LCV [64]. Another interesting case report is a patient who presented with the features of a cocaine/levamisole vasculitis who developed unexpected sudden peritoneal bleed due to an omental artery aneurysmal rupture [65].

Hydralazine

Hydralazine is known to cause a form of drug-induced lupus (DIL). It is defined as a patient who fulfills at least one SLE criteria in the presence of an ANA and/or other autoantibodies without clinical or histological evidence of vasculitis [66]. It has also been associated with an ANCA-positive vasculitis. Renal, pulmonary, or a combination of both with occasional skin involvement has been highlighted in reports. The renal disease is usually a crescentic pauci-immune glomerulonephritis, and the pulmonary involvement is alveolar hemorrhage. The laboratory studies include a positive ANA, positive ANCA, occasional dsDNA autoantibodies, low complement levels, and anticardiolipin antibodies. Specific autoantibodies to neutrophil cytoplasmic components can be directed to elastase or lactoferrrin and sometimes to both [67]. Recent single case reports describe a similar clinical and serological profile [68–70].

Minocycline

Minocycline is a broad-spectrum long-acting bacteriostatic antibiotic derived from tetracycline and used for the treatment of acne vulgaris. Because of its immunomodulating properties, it has also been used, with some success, in the management of rheumatoid arthritis [71]. On the other hand,

minocycline can induce a breach of immune tolerance and cause disease manifestations including serum sickness, drug-induced lupus, autoimmune hepatitis, eosinophilic pneumonitis, and vasculitis [72].

An interesting single-center case series of hepatitis B-negative patients from the Mayo Clinic describes nine patients on minocycline who developed a PAN-like vasculitis. Four patients presented with nonspecific findings of fever, chills, myalgias, arthralgias, and rash, while five patients presented with systemic features without skin involvement. There were testicular pain in three of four men, paresthesias in four patients, and a foot drop in one person. Two patients presented with new onset hypertension. All were MPO-ANCA positive. Three patients were also ANA positive and one had positive dsDNA autoantibodies. Three patients demonstrated a medium-sized vessel vasculitis on angiography, and six patients had a positive skin biopsy for necrotizing vasculitis of muscular arteries [73•]. Cutaneous PAN has been described rarely affecting organs beyond the skin. Improved imaging techniques and increased awareness of multi-organ involvement of DIV suggest that systemic involvement is not uncommon.

A 28-year-old patient who had been on minocycline for only 2 weeks developed left leg weakness and paresthesias without a rash. She had a positive sural nerve biopsy with perivascular inflammatory cell collections in both the endoneurium and ipeneurium. After discontinuation of the minocycline, the patient regained strength and a normal gait [74]. Another case report presented a patient who developed testicular pain and abdominal discomfort after being on minocycline for 12 months. Ultrasonography demonstrated an intratesticular hypoechoic lesion with a hyperechoic area that corresponded to an infarction. No rash was present. A positive ANCA was found [75]. An ANCA- and ANA-positive 21-year-old patient presented with Raynaud-like bluish discoloration of his fingertips, weight loss, left testicular and abdominal, arthritis, and arthralgias after being on minocycline for 2 years. Testicular biopsy revealed medium-size vessels with arteritis, and the angiogram showed scattered aneurysms in the kidney and in the splenic circulation [76]. These patients present with a PAN-like illness with ANCA positivity in most cases, in contrast to classic PAN with an ANCA positivity of only 6.7 % [77].

Rituximab

Rituximab is a monoclonal antibody directed to the CD20 antigen on the surface of B cells that clears them from the peripheral blood. It does not affect plasma cells or the B cell line in lymphoid tissue. Rituximab has become an important treatment option for the management of ANCA-associated vasculitis [78] and yet can be the cause of vasculitis [79, 80]. The presentation is primarily cutaneous with purpuric lesions with hemorrhagic vesicles and which on biopsy show LCV [81].

A particularly challenging case was a 65-year-old patient with idiopathic AAV (GPA) who developed pancytopenia while on cyclophosphamide and was switched to rituximab after new cavitating lesions and active urine sediment were found. In the context of falling PR3-ANCA levels, the absence of diminishing cardiac function, negative cultures, and coverage with broad-spectrum antibiotics, it was assumed to be a rituximab pneumonitis and was treated with high-dose glucocorticoids with sufficient recovery to be able to leave the hospital [82]. Six of 22 cases of cryoglobulinemic vasculitis associated with hepatitis C developed a flare of the cutaneous disease when treated with rituximab. Three patients had severe cutaneous manifestations and all had some systemic involvement including the heart, gastrointestinal tract, and acute neuropathy thought to be mononeuritis multiplex. IgMκ-mixed cryoglobulins complexed with rituximab induce severe systemic reactions. High cryoglobulin levels (>1.00 g/L) and low C4 serum levels (<0.03 g/L) should raise concern about using rituximab for cryoglobulinemic vasculitis [83].

Montelukast (Leukotriene Receptor Antagonists)

Cysteinyl leukotriene receptor antagonists (zarfilukast, montelukast, and pranlukst) (LTRA) are used as steroid-sparing agents for the treatment of asthma. More than 100 cases of eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome or allergic granulomatosis, have been reported. Pulmonary infiltrates, eosinophilia, and cardiac, neurological, and skin involvements are the characteristic features. Montelukast exposure in asthmatic patients is associated with a 4.5-fold higher risk of developing EGPA [84]. It is unclear if preexisting EGPA is unmasked as treatment is modified when the glucocorticoids are tapered as the LTRA is added [85].

Two of three cases of Churg-Strauss syndrome which developed during montelukast therapy, manifested by a purpuruc rash. A third patient demostrated liver and scleral involvement. Two of the three cases were ANCA negative but responded well to the discontinuation of the LTRA [86].

Statins

Statins are 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors that have a profound effect on hypercholesterolemia and in the prevention of coronary heart disease, cardiovascular risk factors, and cerebrovascular and peripheral vascular disease [87]. Hepatic dysfunction and muscle injury are the primary adverse events; however, a few reports of autoimmune reactions such as a dermatomyositis-like syndrome, a lupus-like syndrome, and an interstitial lung disease have been described [88]. Vasculitis

can be added to the adverse events seen with statins, which manifest with rash showing features of LCV, myalgias, arthralgias/arthritis, and peripheral neuropathy [89]. Another case report presented a patient with abdominal pain, a purpuric rash, and a skin biopsy with LCV and IgA deposition. Imaging of the GI tract, using several imaging modalities (ultrasonography; oral, intravenous, and rectal contrast-enhanced whole abdominal CT scan, and contrast-enhanced abdominal MRI) showed bowel wall thickening and vascular engorgement. This was compatible with inflammatory vasculitic bowel involvement [90]. Two of these three cases had exposure to the statin at 3 weeks and at 2 months prior to the disease appearance and only one of the three cases was ANCA positive.

Approach

It cannot be stressed enough that a high index of suspicion on the part of the clinician is mandatory. Although uncommon, the recognition of a DIV is a source of great satisfaction for the physician. It is the result of a careful and a thoughtful approach to the patient. A management strategy of restraint with the simple discontinuation of the offending agent is usually sufficient. At worse, a temporary course of glucocorticoids and immunosuppressants suffices. It is worth noting that an alternative treatment modality exists even within the same category of therapeutic agents and, of course, in unrelated categories as well.

The differential diagnosis of DIV includes infections, malignancies, and idiopathic vasculitis, and they should be considered first. This should be followed by a careful medication history with attention to over-the-counter alternative medications and illicit drugs. One must consider the temporal relationship between the therapeutic agent and the clinical presentation. A bewildering number of therapeutic agents have been implicated in DIV, many based on single case reports, often with limited information to support the relationship. A review of the published literature, nevertheless, may bring to the forefront candidates implicated in DIV. A review of the most recent literature can identify newer agents suspected of causing DIV.

The clinical presentation can be nonspecific with fever, myalgias, arthralgias, and weight loss. It can be related to a skin rash alone, but careful evaluation of all organ systems particularly the lung, kidney, liver, and neurological system may show multi-systemic involvement. The presence of serological abnormalities (ANA, ANCA, antiphospholipid antibodies, dsDNA autoantibodies, low complement levels) may suggest a confusing autoimmune disorder but in the proper setting would arouse suspicion of a DIV.

The presence of ANCA based on the indirect immunofluorescence technique (IIF) is particularly important and should always be followed by a search for specific antibodies against PR3 and MPO. The absence of these specific antibodies in the face of a positive IFF may be due to antibodies to other neutrophilic enzymes such as elastase, lactoferrin, cathepsin B, and lysozyme among others. Unfortunately, testing for these specific enzymes is not commercially available. ANCA positivity may occur with many drugs and is particularly well documented with long-term (>18 months) use of PTU, where 26.7 % of patients develop a positive ANCA but few patients develop vasculitis [91]. It would be inappropriate to stop treatment based on seroconversion alone although careful subsequent clinical monitoring is appropriate.

Central pillars in the diagnosis of DIV include a positive histopathologic finding in the affected tissue and suggestive vascular imaging. Fortunately, the skin is the commonly involved and readily available tissue. It will show LCV, sometimes with a strong thrombotic component. Kidney biopsy can show a crescentic GMN with scant immune complex deposition. Other organs that can be biopsied include the lung, liver, and peripheral nerves. Advances in imaging can help evaluate the organs involved and show tissue infarcts, edema, and vascular anomalies supporting the presence of a multisystemic disease compatible with vasculitis. Finally, a common thread is that discontinuation of the suspect agent will usually lead to resolution the clinical disorder (Table 2). A rechallenge with the same agent is rarely necessary, as reasonable alternative agents exist.

Treatment

The course of DIV is very different from idiopathic vasculitis with an overall better outcome if recognized early. Simply discontinuing the offending agent can resolve the illness. Aggressive management is reserved for those with serious organ

Table 2 Approach to the diagnosis and evaluation of drug-induced vasculitis

High index of suspicion
Differential diagnosis—r/o infection, malignancy, idiopathic vasculitis
Careful drug history
Review literature for comprehensive and agent-specific reports
Serological studies (ANA, ANCA (IIF and ELISA technique) antiphospholipid antibodies, dsDNA, C3 and C4 complement levels)
Biopsy (skin, affected organs)
Imaging (MRA, CT, angiography, ultrasonography)
Discontinuation of suspected agent and close subsequent follow-up

ANA antinuclear antibodies, *ANCA* antineutrophil cytoplasmic antibodies, *IIF* indirect immunofluorescence technique, *ELISA* enzyme-linked immunosorbent assay, *dsDNA* double-stranded DNA, *MRA* magnetic resonance imaging, *CT* computed tomography

involvement as side effects of immunosuppression are considerable. The first step is to discontinue the offending agent. For those with severe and active organ involvement, prednisone at 1 mg/kg for 1 to 2 months with subsequent tapering is required. For significant renal and respiratory failure associated with alveolar hemorrhage, cyclophosphamide or other immunosuppressants (mycophenolate mofetil or rituximab) may be added. Supportive care would include ventilatory support and renal dialysis and plasmapheresis for pulmonary hemorrhage. Pulse methylprednisolone of 1 g a day for 3 days can be used in early life-threatening cases.

The individual course is not predictable and each patient will need to be monitored carefully. It is important to note that the serological abnormalities may persist for 12–24 months without clinical indication of an ongoing organ damage [11]. Fatalities are due to delay or error in diagnosis.

Conclusions

Although not common, DIV must be considered in every patient with a vasculitic presentation. Recognition and management is gratifying, and many times discontinuing the offending agent is sufficient. Biological agents have become an important cause of DIV and most likely will be seen more frequently in the future.

Expanded categories of vasculitis from the 2012 Chapel Hill Consensus Conference now recognize drug-mediated vasculitis among the vasculitides associated with known etiology as being an immune complex-related or ANCA-related condition. A classification criteria is the next step to create homogenous study groups. Important advances in epigenetics and genetics may help identify susceptible individuals to DIV. MicroRNAs in vascular endothelial cell activation may be an important area to explore in vasculitis. Released nuclear chromatin traps (NETs) from granulocytes are a newly discovered and relevant form of cell death called NETosis. This phenomenon detected in kidney biopsies from patients with ANCA-associated vasculitis and the demonstration that PTU alters the characteristics of these NETs may add insights into the pathogenesis of DIV and idiopathic vasculitis. The next years will be an exciting time for our understanding of vasculitis in general.

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Compliance with Ethical Standards

Conflict of Interest The author declares that he has no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any information derived directly from human or animal subjects.

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- •• Of major importance

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