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Drug-Induced Renal Vasculitis: Etiology, Pathogenesis, Clinical Manifestations, and Therapeutic Approaches—A Narrative Review

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ABSTRACT

Background and Aims: Drug-induced renal vasculitis arises from various medications that cause immunological dysregulation or direct vascular damage, leading to inflammation and thrombosis. Clinical manifestations vary widely, from mild constitutional symptoms to severe organ dysfunction. This review aims to thoroughly explore drug-induced renal vasculitis, focusing on its etiology, pathological mechanisms, clinical manifestations, diagnostic challenges, and therapeutic approaches. This review aims to summarize current knowledge and highlight areas requiring further research.

Methods: A comprehensive literature search was conducted using PubMed, MEDLINE, Embase, and Cochrane Library databases. We included peer-reviewed journal articles and excluded those with insufficient data, poor quality, or lack of relevance. The search terms included combinations of "renal vasculitis," "drug-induced vasculitis," "drug-related nephritis," "medication-induced renal vasculitis," and specific drug names. An initial search yielded 13,192 articles, of which 13,103 were excluded due to irrelevance, duplication, or outdated information. After full-text review, 99 peer-reviewed articles were included.

Results: Discontinuation of the offending drug is the primary and most crucial step in managing drug-induced renal vasculitis. Prognosis is generally more favorable than primary vasculitis, with a high remission rate if the offending drug is stopped early. Due to its rarity, epidemiological data is limited. Diagnosis frequently relies on autoantibodies [antineutrophil cytoplasm antibodies (ANCA), myeloperoxidase (MPO), antinuclear antibody (ANA)] and clinical symptoms, with renal biopsy confirming it. Factors such as high-dose and long-term drug use, as well as genetic predispositions, increase the risk.

Conclusion: This review provides a comprehensive overview of drug-induced renal vasculitis, discussing what is known and identifying gaps in understanding. While discontinuing the causative drug remains the cornerstone of management, further research is needed, particularly in developing a formal tool to assess the quality of studies and minimize selection bias.

1 | Introduction

An inflammatory process of blood vessels caused by the use of numerous pharmacological drugs is known as drug-induced vasculitis [1]. Consistent long-term pharmacological treatment seldom results in the development of a widespread medication-induced illness, although skin vasculitis is a common side effect [2, 3]. Numerous medicinal substances have the potential to negatively impact the kidney, leading to blood vessels, renal, or tubulointerstitial illness.

The use of antibacterial agents and pain-relieving medicinal products is the primary cause of drug-induced renal vasculitis [4]. The following medications have also demonstrated unambiguous evidence of a relation to the emergence of drug-induced vasculitis: hydralazine, tumor necrosis factor (TNF) inhibitors, sulfasalazine, D-penicillamine, and minocycline [5–13]. Clinically, it presents identically to primary anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV); however, it may be differentiated from primary AAV by the presence of multiantigenic ANCA [14]. When drug-induced AAV is diagnosed, the offending medications should be discontinued right away. This review aims to thoroughly explore the relationship between drugs leading to renal vasculitis by explaining the pathophysiological mechanisms, presenting symptoms, and diagnostic features to increase our understanding. It could lead to more effective methods for drug-induced vasculitis detection and management.

2 | Methods

A comprehensive literature search gathered relevant studies on drug-induced renal vasculitis. The primary databases searched included PubMed, MEDLINE, Embase, and Cochrane Library. We included peer-reviewed journal articles and omitted those with insufficient data, poor quality, or lack of relevance to our title. Search terms included combinations of "renal vasculitis," "drug-induced vasculitis," "drug-related nephritis," and specific drug names known to be associated with renal vasculitis. The full text of the selected articles was then reviewed for final inclusion in this study.

During the initial search, 13,192 articles were identified using specific keywords and search terms. 13,103 articles were excluded for the following reasons:

1. Most articles do not align with the review objectives, primary title, and abstract.
2. Duplicate publications or studies with overlapping data were excluded, too.
3. Newer and advanced studies were preferred over older studies.
4. Studies irrelevant to the primary title and abstract were excluded, too.

Ultimately, 10 articles from peer-reviewed journals were included [15–24]. In total, 99 articles were selected for this review. The search terms included combinations of "renal vasculitis," "drug-induced vasculitis," "drug-related nephritis," and specific drug names associated with renal vasculitis.

The review discusses common themes, identifies gaps in the current knowledge, and highlights areas for future research.

3 | Antibiotics

Antibiotic-induced renal vasculitis is a serious and rare complication; several antibiotics have been linked to renal vasculitis, including cefotaxime, minocycline, nitrofurantoin, trimethoprim/sulfamethoxazole, vancomycin, ciprofloxacin, doxycycline, and anti-tuberculosis (TB) drugs like isoniazid and rifampicin [25]. Details on the different cases are mentioned in Table 1. Unfortunately, the rarity of this condition makes it difficult to predict its prevalence through epidemiological data [25]. Drug-induced vasculitis has a higher remission rate if the offending drug is stopped and, if necessary, the patient is given corticosteroids [15].

Few cases of ciprofloxacin-induced renal vasculitis have been reported in the literature. In 1995, Shih and colleagues reported two cases: one ANCA-positive with normal glomeruli and necrotizing arteritis, while the other was ANCA-negative with segmental glomerular necrosis and fibrinoid changes. Both patients improved after stopping ciprofloxacin and were treated with corticosteroids and cyclophosphamide [33]. Storsley and Geldenhuys presented a case of ANCA-negative renal vasculitis, and their biopsy showed glomeruli with diffuse cellular proliferation, crescents, moderate cellular infiltrate within the interstitium, and red blood casts within the tubules [26].

Doxycycline and minocycline are commonly prescribed tetracycline antibiotics in the United States. With over 5 million doxycycline prescriptions annually, cases of doxycycline-induced renal vasculitis are rare [28]. According to our knowledge, the first case of ANCA-negative isolated renal vasculitis induced by doxycycline was in 2001 by Goland et al. [16] Another case of doxycycline-induced ANCA-positive vasculitis was reported by Wriston et al. [28]. In both cases, the condition improved after discontinuing doxycycline and taking prednisolone.

Minocycline is an effective and widely used tetracycline for acne treatment. Previous case reports have correlated it with cutaneous vasculitis, but it is rarely reported as a cause of renal vasculitis [29]. Kermani and colleagues reported a case series that identified nine patients developing minocycline-induced polyarteritis nodosa (PAN)-like vasculitis. Complications started after minocycline use for 1–4 years, with only two having renal involvement. All cases were perinuclear antineutrophil cytoplasmic antibodies (p-ANCA positive), and minocycline was discontinued for all of them [34]. Sethi and colleagues reported a case of minocycline-induced severe pauci-immune crescentic and necrotizing glomerulonephritis with positive cytoplasmic ANCA and proteinase 3 (PR3). The offending drug was discontinued, and the patient was started on immunosuppressive medication [13].

TABLE 1 | Reported cases of antibiotic-induced renal vasculitis/crescentic glomerulonephritis.

Drug class	Drug name	Case reference	Age/ gender	Duration since therapy initiation	Autoantibodies present	Was the drug discontinued	Treatment	Outcome
Cephalosporin	Cefotaxime	Feriozzi et al. [17]	65 y/M	6 days	p-ANCA, MPO	Yes	Discontinue medication only	Condition improved
Fluoroquinolones	Ciprofloxacin	Storsley and Geldenhuys [26]	50 y/M	10 days	Negative	Yes	Prednisone	Condition improved
DHFR inhibitor-sulfonamide	Trimethoprim-sulfamethoxazole	Hegde et al. [27]	60 y/M	2 weeks	Negative	Not provided	Plasmapheresis, corticosteroids, cyclophosphamide, hemodialysis	Patient expired
Nitrofurantoin	Nitrofurantoin	Agarwal et al. [18]	67 y/F	3 days	P-ANCA, MPO	Yes	Prednisone	Condition improved
Tetracycline	Doxycycline	Goland et al. [16]	42 y/F	2 days	Negative	Yes	Prednisone	Condition improved
		Wriston et al. [28]	56 y/F	18 days	ANA, pANCA, MPO	Yes	Prednisone	Condition improved
	Minocycline	Tabriziani et al. [29]	21 y/F	2 years	ANA, p-ANCA, MPO	Yes	Prednisone and cyclophosphamide	Condition improved
Anti TB	Rifampicin	Kistler et al. [30]	69 y/F	2 weeks	Negative	Yes	Corticosteroids	Condition improved
		Ji et al. [31]	42 y/F	5 days	PR3-ANCA	Yes/rechallenge failed	Prednisone	Condition improved
	Isoniazid	Brik et al. [32]	13 y/F	1 month	Negative	Yes	Corticosteroids and cyclophosphamide	Condition improved
	Antitubercular therapy (ATT)	Kumar et al. [19]	49 y/M	1 month	p-ANCA, anti-GBM	Yes	Plasmapheresis, corticosteroids, cyclophosphamide, hemodialysis	Patient expired due to rapidly declining renal function

4 | Antitumor Necrosis Factor Alpha Medications

Adalimumab, infliximab, and etanercept belong to the anti-TNF alpha class of drugs widely used to treat chronic inflammatory conditions. However, ~10% of patients may develop autoantibodies such as anti-double-stranded DNA (anti-dsDNA), anticardiolipin, and antinuclear antibodies (ANA) after prolonged use of these medications. Although rare, few patients on anti-TNF-α agents can develop vasculitis [1, 25, 35]. Etanercept is the most common drug that causes renal alterations, followed by Adalimumab and Infliximab. These alterations can appear as isolated manifestations or as part of more complex disorders such as systemic vasculitis or SLE. Different types of vasculitis with renal involvement have been described, such as AAV and IgA vasculitis (formerly known as Henoch–Schönlein purpura) [35].

Various theories for anti-TNF alpha drug-induced vasculitis have been formulated. According to the cytokine shift paradigm, blocking TNF-α suppresses Th1 cytokines and promotes Th2 cytokine production, leading to autoantibody production and lupus manifestations. Anti-TNF-α drugs may induce apoptosis in inflammatory cells, releasing autoantigens that stimulate autoantibody formation [36].

Piga and colleagues conducted a thorough review and analysis of a group of patients to investigate the development of autoimmune renal disease resulting from biological treatment, including TNF-α inhibitors. The study identified 26 patients who experienced symptoms 6 months after starting their medication. More than 50% of the patients took etanercept, followed by adalimumab and infliximab, and around 45% of the patients had a diagnosis of isolated autoimmune renal disorders, followed by glomerulonephritis associated with systemic vasculitis and glomerulonephritis in a lupus-like syndrome. The symptoms resolved in 1–4 months after stopping the drug [37]. Kaneko and colleagues have reported two cases of etanercept-induced necrotizing crescentic glomerulonephritis [38]. Additionally, the retrospective review presented by Stokes and colleagues showed five cases where all patients received different anti-TNF therapies, resulting in renal disease [7]. For more details on different cases, refer to Table 2.

The first step in treating drug-induced vasculitis is to stop the offending drug. Treatment is typically based on primary vasculitis guidelines, but due to limited data, treatment is customized for each patient. Patients with worsening renal function or pulmonary involvement can be started on corticosteroids and/or other immunosuppressive drugs like cyclophosphamide and rituximab [1, 39].

If TNF inhibitor-induced vasculitis occurs, consider using an alternative class agent and monitor carefully, as there have been reports of recurrence after changing the anti-TNF agent. Przygocka and colleagues reported a case in which a patient developed renal-limited IgA vasculitis after taking adalimumab. When adalimumab was reintroduced, vasculitis reoccurred, leading to the permanent discontinuation of adalimumab [39].

TABLE 2 | Reported cases of glomerulonephritis due to anti-TNF therapy.

Case reference	Anti-TNF alpha drug taken	Duration since therapy initiation	Autoantibodies present	Was anti-TNF discontinued	Treatment	Outcome
Kaneko et al. [38]	Etanercept	28 months	ANA, MPO-ANCA	Yes	Corticosteroids	Condition Improved
Kaneko et al. [38]	Etanercept	18 months	Negative	Yes	Corticosteroids	Condition improved
Stokes et al. [7]	Etanercept	4 months	ANA, MPO-ANCA	No	Intravenous cyclophosphamide	Patient expired
Stokes et al. [7]	Infliximab	10 months	Negative	Yes	Corticosteroids and intravenous cyclophosphamide	Condition improved
Stokes et al. [7]	Etanercept	6 months	Negative ANCA	Yes	Oral prednisolone and cyclosporine	Condition improved
Przygocka et al. [39]	Golimumab	6 years	Negative ANCA	Yes	Corticosteroids and rituximab	Condition improved
Przygocka et al. [39]	Adalimumab	Not mentioned	Negative	Yes	Corticosteroids and rituximab	Condition improved

5 | Psychoactive Agents

Levamisole is a drug that treats parasite infections and functions as an immunomodulatory agent. It is increasingly being used as an additive in cocaine. It is estimated that ~70% of the cocaine consumed in the USA now contains levamisole [20]. The drug functions as a hapten due to reactive thiol groups in its structure. It causes immunological responses that encourage the maturation of dendritic cells, the release of proinflammatory cytokines, the creation of autoantibodies, and cytotoxicity [40, 41]. Vasculitis, necrosis, and intravascular thrombosis are caused by adverse effects of levamisole in various organs and tissues, including the skin, kidneys, brain, and hematological system. Cocaine's nephrotoxic effects, which include altered intrarenal hemodynamics, oxidative stress, the formation and breakdown of extracellular matrix, and renal atherogenesis, can also cause renal damage [42–46].

The most notable association between AAV and cocaine use is that the condition can cause arthralgias, cutaneous necrotizing vasculitis, and constitutional symptoms. This correlation may be seen in the presence or absence of crescentic GN, pauci-immune localized necrotizing and pulmonary bleeding. Anti-PR3-ANCA is found in at least half of patients, but anti-myeloperoxidase (MPO) ANCA is serologically detectable in almost all patients. In actuality, exposure to levamisole-laced cocaine is now pathognomonic for positivity for PR3- and MPO-ANCA [45].

Cocaine and levamisole have short elimination half-lives (0.7–1.5 and 5–6 h, respectively), making it difficult to detect these drugs in bodily fluids [46]. Levamisole is detectable for up to 3 days following exposure, especially when using gas chromatography/mass spectrometry testing [47]. Cocaine should be detected in the urine of any patient who has been diagnosed with suspected ANCA vasculitis; if the test is positive, levamisole should also be checked in the patient's urine [45].

In a case report by Veronese and colleagues, a kidney biopsy revealed 25 glomeruli, 8 of which had intraglomerular necrosis and cellular crescents. There were no globally sclerosed glomeruli. In addition, widespread and persistent inflammatory infiltration in the tubulointerstitium, localized mesangiolysis, interstitial fibrosis and tubular atrophy, and podocyte hypertrophy were observed in 10% of the total cortical area. There were no immunofluorescence results for IgG, IgM, IgA, C1q, C3, fibrinogen, kappa, or lambda, consistent with pauci-immune crescentic glomerulonephritis.

Levamisole-tainted cocaine was linked to retinal purpura, crescentic glomerulonephritis, and positive anti-MPO and anti-PR3 antibody tests. Anti-myeloperoxidase (anti-MPO) antibody 109 IU/mL (positive if > 5 IU/mL) and anti-PR3 antibody 35 IU/mL (positive if > 10 IU/mL) were both anti-ANCA tests that yielded positive results (titers > 1:320). The results of the renal ultrasonography were normal [48]. Pulse therapy utilizing intravenous methylprednisolone followed by oral prednisone, along with oral or intravenous cyclophosphamide and occasionally plasmapheresis, has been employed because of parallels with approaches to treat primary AAV [46].

Levamisole is included in this discussion because it is used as a contaminant in cocaine and has a great appreciation as a cause of AAV. In a case report by Moinuddin and colleagues, a woman with cocaine and subsequent levamisole exposure developed anti-MPO AAV. Besides findings of crescentic GN, the patient also had biopsy evidence of secondary membranous nephropathy [49]. Another case series by Collister and colleagues describes three cases where levamisole-adulterated cocaine was associated with AAV, which was further associated with membranous nephropathy [50]. Thus, this highlights the association of these old drugs with renal vasculitis and subsequent renal pathologies, which warrants further research and also highlights the fact that these drugs should be considered when dealing with such pathologies.

The cornerstones of treating cocaine's nephrotoxic consequences, including levamisole-adulterated cocaine-induced ANCA vasculitis, are blood pressure control, immediate cessation of the causative agent, and supportive treatment directed at the apparent nephrotoxic effects. Immunosuppression is a typical supplementary therapeutic option for levamisole-adulterated cocaine-induced ANCA vasculitis, depending on the severity of the illness [45].

6 | Antiepileptics

Although phenytoin is a commonly used anticonvulsant, it has been cited occasionally in the past few decades as an uncommon medicine that can cause AAV, which is frequently fatal [21, 48, 51]. The 65-year-old male patient reported by Park and colleagues had AAV brought on by phenytoin, and he fared well after stopping the medication and receiving immunosuppressive therapy [21].

7 | Antithyroid Medications

Vasculitis is a rare complication of antithyroid medication therapy, but other common side effects include arthralgias, leukopenia, skin rash, and a slight increase in liver enzymes [52, 53]. Compared to PR3, autoantibodies against MPO are more prevalent [54]. Anti-MPO antibody titers are likely drug-related, particularly after taking propylthiouracil (PTU) or hydralazine [55].

Although the findings suggest that a significant fraction of ANCA-positive vasculitis cases with high precise percentages have not been released, it is said that MPO-ANCA is more commonly found in MPO-ANCA-related vasculitis due to PTU than in that caused by methimazole [56]. It has also been documented that people with PTU-induced AAV have significantly increased anti-MPO antibody titers and affinities than ANCA-positive patients who do not develop vasculitis [57].

According to studies, the length of antithyroid drug (ATD) is correlated with ANCA production. Therefore, patients on PTU for longer than 18 months should monitor their serum ANCA levels closely, and longer than 3 years is not advised for PTU use [22, 58]. Repeated administration of PTU has been shown by

Lee and colleagues to partially alter the structure of MPO [59]. Jiang and colleagues proposed that PTU may act as an MPO precursor and that the metabolites may cause unusual reactions to immunity by exposing autoreactive lymphocytic cells to aberrant forms of self-material [60].

A cross-sectional analysis of 207 patients with hyperthyroidism in the Netherlands suggested an 11.8-fold higher odds (95% confidence interval, 1.5–93.3) of developing a reactive ANCA serology (p-ANCA, cytoplasmic ANCA, or atypical p-ANCA on immunofluorescence or ELISA positive for anti-MPO, PR3, or human lactoferrin antibody) [61]. Withdrawing the harmful agent is the primary step in management, which has remained the same in recent years. However, raising awareness and alertness of drug-induced vasculitis can result in an earlier diagnosis, preventive measures against severe damage to body organs, and even avoidance of fatal deaths [62].

8 | Hydralazine

Hydralazine, a vasodilator used to treat hypertension, is often combined with beta-blockers and diuretics to manage side effects such as reflex tachycardia and fluid retention [63]. Although generally considered safe, there have been rare but severe reports of hydralazine-induced vasculitis, first noted in the skin in 1980, followed by renal vasculitis in 1981 [64–66]. By 1983, cases of rapidly progressive glomerulonephritis (RPGN) began to surface, highlighting the condition's severity [5, 67].

The risk of hydralazine-induced vasculitis appears to be dose-dependent, with reported incidences of 5.4% at 100 mg/day and 10.4% at 200 mg/day when used for more than 3 years [68, 69]. Identified risk factors include female sex, thyroid disease, high doses of hydralazine, and a slow acetylator status [70]. Slow acetylators, with reduced N-acetyltransferase activity, are less able to metabolize hydralazine, which may lead to immune dysregulation [71, 72].

This condition predominantly affects the kidneys and skin but can also impact the lungs, joints, and nerves [66]. Clinically, it mimics idiopathic ANCA-associated small-vessel vasculitis, manifesting symptoms similar to granulomatosis with polyangiitis, microscopic polyangiitis, or eosinophilic granulomatosis with polyangiitis [64]. Patients often present with rapidly progressive necrotizing glomerulonephritis, which can include joint pain, pleuropulmonary disease, and skin involvement [45].

The diagnosis of this condition can be aided by the presence of specific antibodies, including high levels of MPO ANCA, ANA, antihistone antibody, antielastase antibody, and antiphospholipid antibody [60, 73]. Unlike AAV, drug-induced vasculitis is commonly associated with antihistone antibody. To support the diagnosis of hydralazine-induced vasculitis in patients with evidence of pauci-immune glomerulonephritis, a combination of antihistone antibody, MPO and/or PR3 ANCA, anti-dsDNA antibody, and hypocomplementemia can be used in a clinical setting [1]. In cases where hydralazine is implicated in the developing ANCA vasculitis, there may be varying degrees of tubular atrophy, interstitial fibrosis, interstitial inflammation, and tubular degenerative changes. This autoimmune response is a defining characteristic of ANCA-mediated glomerulonephritis in the context of hydralazine use [74].

It is still unclear how hydralazine could contribute to the emergence of ANCA vasculitis, although some intriguing indications exist. Patients with ANCA vasculitis display abnormal levels of specific proteins, including MPO and PR3, in their neutrophils, which are thought to be caused by epigenetic modifications in the genes responsible for these proteins [75–78]. This abnormality is linked to a lack of the histone marker H3K27me3, typically associated with gene suppression. This deficiency appears to be the result of higher levels of JMJD3 demethylase and the inability of Runt-related Transcription Factor 3 (RUNX3) to recruit Enhancer of Zeste Homolog 2 (EZH2), an enzyme involved in the methylation of the H3K27me3 marker [78]. Along with its known effects on lowering blood pressure, hydralazine also functions as a synthetic non-nucleoside DNA methylation inhibitor [79, 80]. Essentially, by inhibiting DNA methylation, hydralazine could potentially interfere with the normal epigenetic control of MPO and PR3 genes, potentially intensifying the autoimmune response in ANCA vasculitis.

A study by Timlin and colleagues highlighted the severity of hydralazine-induced vasculitis in a cohort of patients. In their analysis, all patients showed significant organ involvement at diagnosis, and although stopping hydralazine alongside immunosuppressive therapy induced remission, many had poor renal outcomes. Out of seven patients in the study, three progressed to end-stage renal disease despite treatment with steroids, cyclophosphamide, and plasma exchange. Notably, the presence of both ANA and p-ANCA was universal, and most patients had elevated MPO-ANCA levels [81].

Treatment begins with discontinuing the drug. This may be sufficient for recovery in mild cases, but severe cases often require immunosuppressive therapy, such as corticosteroids, cyclophosphamide, or rituximab [69, 82, 83]. However, even with treatment, patients may face ongoing complications, including chronic renal damage and the need for dialysis, with recovery being variable [68, 84, 85].

9 | Allopurinol

Allopurinol (4-hydroxypyrazole-[3,4-d] pyrimidine), an inhibitor of xanthine oxidase enzyme, is currently being used for disorders of uric acid metabolism. Allopurinol is well known for its hypersensitive cutaneous manifestations [86]. The HLA-B*5801 allele is a risk factor for skin hypersensitivity reaction to allopurinol in Asian populations [86]. Renal hypersensitivity vasculitis was observed in some cases. A case of renal vasculitis due to allopurinol overdose was seen in a Chinese patient taking allopurinol [87]. Following coronary artery bypass grafting, another case of renal hypersensitivity vasculitis was noted as a result of allopurinol toxicity [23]. Allopurinol hypersensitivity syndrome (AHS) results in the involvement of multiple systems. Singer and Wallace proposed criteria for the diagnosis of AHS [88, 89]. A minimum of two main criteria, or one major and one minor criterion, must be met, as well as a record of allopurinol use and no exposure to other medications

that cause comparable symptoms. Acute liver failure, increasing renal failure, and rash—which manifests as exfoliative dermatitis, erythema multiforme, diffuse maculopapular rash, or toxic epidermal necrolysis—are major requirements. Fever, leukocytosis, and eosinophilia are minor requirements [89]. Occasionally, allopurinol can also cause DRESS syndrome, which can result in acute renal damage. Kidney biopsies in these individuals showed necrotizing vasculitis of the interlobular arteries and eosinophilic tubulointerstitial nephritis [90].

10 | D-Penicillamine

Like allopurinol, evidence is available that D-penicillamine can also result in skin reactions and renal vasculitis [24]. D-penicillamine can result in AAV, which may result in RPGN or pulmonary renal syndrome [91]. A 13-year-old child with Wilson disease who took D-penicillamine for 5 years was reported to have pulmonary renal syndrome [91]. Another case reported the development of anti-MPO antibodies in a patient taking D-penicillamine, further leading to renal vasculitis [11]. It is thought that, like allopurinol, penicillamine nephropathy may also be associated with HLA B 8 alloantigen. A total of 33 patients who developed renal nephropathy while taking D-penicillamine for rheumatoid arthritis were the subject of a long-term investigation. Twelve of the 33 patients experienced proteinuria. However, 6 months after the medication was stopped, the proteinuria went away on its own. In total, 29 patients had membranous glomerulonephritis, 2 had minimal change nephropathy, and 2 had electron-dense deposits in the mesangial areas upon renal biopsy [92].

11 | Aminosalicylates

Aminosalicylates, including sulfasalazine and mesalamine (5-ASA), are also seen to be causing renal vasculitis. Although the exact etiology of nephrotoxicity in individuals with inflammatory bowel disease (IBD) receiving 5-ASA is unknown, renal damage has been observed in as many as 1 in 100 patients getting this treatment [93]. Renal vasculitis caused by 5-ASA typically manifests within the first 12 months but can also occasionally emerge years later. The risk of nephrotoxicity and the dosage of 5-ASA are not correlated, making this consequence idiosyncratic rather than dose-related [94]. The possibility for mesalazine and sulfasalazine to cause renal damage is similar. When a patient with IBD exhibits a loss in renal function, mesalazine must be stopped; a renal biopsy should be performed if this does not cause a drop in serum creatinine. Patients whose renal function does not improve with medication discontinuation are also administered steroids [95].

12 | Possible Mechanisms for ANCA-Associated Vasculitis (AAV)

There are some potential mechanisms behind AAV. An article by Lenka and colleagues states that the mechanisms by which ANCA antibodies cause vasculitis involve excessive neutrophil activation, which subsequently leads to the release of proinflammatory cytokines, reactive oxygen species, and lytic enzymes. In addition, activated neutrophils induce the formation of neutrophil extracellular traps in NETosis (neutrophil extracellular trap formation). The released neutrophil antigens are exposed to the immune system via antigen-presenting cells, which further stimulates antibody production and creates a vicious circle of tissue destruction [96]. Thus, a vicious cycle of neutrophil extracellular traps formation and ANCA production is considered to be involved in the pathogenesis of AAV [97].

An article by Massicotte-Azarniouch and colleagues states that ANCA triggers neutrophil activation leading to vascular damage in ANCA vasculitis. However, decades of studies have determined that neutrophil activation alone is not sufficient to cause disease. Inflammatory stimuli perpetuate ANCA autoantigen expression and ANCA production. Genetic and epigenetic alterations of gene encoding for MPO and PR3 provide additional disturbances to the immune homeostasis which provide a substrate for pathogenic ANCA formation from an adaptive immune system predisposed to autoreactivity. Stimulated by inflammatory cytokines, ANCA binding leads to neutrophil activation, a process characterized by conformational changes, production and release of cytotoxic substances, and alternative complement pathway activation, thus creating an intense inflammatory milieu. This cascade of events perpetuates a vicious cycle of further inflammatory cell recruitment and activation, leading to tissue necrosis [98].

12.1 | Clinical Presentation for Adults Versus Pediatric Patients for AVV

The clinical presentation of AAV with kidney involvement often varies between adults and pediatric patients. A review article by Windpessl and colleagues showed that most children with AAV and kidney involvement present with crescentic class (50.6%) (the presence of 50% or more cellular crescents on biopsy specimens). On the other hand, among 145 adult patients with ANCA glomerulonephritis, crescentic class was present in 25.5% of patients. Taken together, the frequency of crescentic class and the recovery in estimated glomerular filtration rates in children exceeds those reported in adulthood, indicating that children present with more acute kidney involvement at baseline but show a higher potential to recover estimated glomerular filtration rates once immunosuppression medication is initiated [99].

An observational study by Monti and colleagues concluded that within 6 months of diagnosis of AAV, patients > 65 years of age display a different pattern of organ involvement and an increased risk of significant damage and mortality compared with younger patients. Younger patients had higher rates of musculoskeletal, cutaneous, and ENT manifestations than older patients. Systemic, neurologic, cardiovascular involvement, and worsening renal function were more frequent in the older-onset group [100].

Thus, the clinical presentation between adults and pediatric patients for vasculitis with kidney involvement/AAV.

13 | Conclusion

Renal vasculitis secondary to drug exposure presents a multifaceted clinical challenge, requiring a comprehensive understanding of its

various dimensions. This article thoroughly explores drug-induced renal vasculitis, delving into its origins, pathological mechanisms, clinical manifestations, diagnostic intricacies, and therapeutic approaches. The etiology of drug-induced renal vasculitis involves various medications that exert their effects through mechanisms ranging from immunological dysregulation to direct vascular damage, culminating in inflammation and thrombosis. Clinical presentation of drug-induced renal vasculitis varies, with manifestations ranging from subtle constitutional symptoms to severe organ dysfunction. Diagnosis relies on clinical suspicion, laboratory investigations, imaging studies, and histopathological examination. Management strategies entail discontinuing offending agents, supportive care, and immunosuppressive therapy in severe cases. Case studies and clinical anecdotes provide valuable insights into the diagnostic and therapeutic challenges of managing drug-induced renal vasculitis. Through increased awareness and understanding, clinicians can navigate the complexities of this condition more effectively, ultimately improving outcomes for affected individuals. Further research is needed to deepen our understanding of the underlying pathophysiology and refine treatment modalities in drug-induced renal vasculitis.

Author Contributions

Hashim Mohamed Siraj: conceptualization, data curation, formal analysis, methodology, resources, supervision, writing – original draft, validation, visualization. **Masab Ali:** writing – original draft, writing – review and editing, visualization, validation, conceptualization, formal analysis, methodology. **Sampda Sanjaykumar Sharma:** data curation, writing – review and editing, writing – original draft, validation, visualization. **Afreen Begum:** data curation, resources, validation, visualization, writing – original draft, methodology. **Muhammad Husnain Ahmad:** validation, visualization. **Hassan Muhammad:** writing – review and editing, formal analysis, visualization, validation. **Roba Kamaleldin Moustafa Kamel Aref Elsayed:** data curation, writing – original draft, visualization, resources. **Muhammad Hamza Tahir:** data curation, writing – original draft, resources, methodology, visualization. All authors have read and approved the final version of the manuscript.

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The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead authors Hashim Mohamed Siraj affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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