



# Levamisole-induced and COVID-19-induced retiform purpura: two overlapping, emerging clinical syndromes

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## Abstract

Levamisole exposure in cocaine users is a well-recognized cause of retiform purpura, a distinctive net-like maculopapular patch. Prolonged exposure to levamisole can lead to a serious systemic syndrome known as levamisole-induced vasculitis, most commonly involving the kidneys and lungs. More recently, retiform purpura has been observed in patients with the novel coronavirus disease of 2019 (COVID-19). Due to their overlapping dermatologic and systemic manifestations, levamisole-induced and COVID-19-induced retiform purpura may mimic one another in clinical presentation. The possibility that patients may present with one or both syndromes creates a diagnostic challenge. This review of levamisole-induced and COVID-19-induced retiform purpura highlights their corresponding and distinctive features. Additionally, we propose a unique staging system for levamisole-induced retiform purpura that may be valid for future classification of COVID-19-induced retiform purpura.

**Keywords** Levamisole · Cocaine · Vasculitis · Retiform purpura · COVID-19 · Neutrophils · Drug abuse

## Introduction

Over the last 10 years, retiform purpura has been extensively observed in patients exposed to levamisole-contaminated cocaine. While patients are often first evident with cutaneous manifestations, end-organ disease may occur as well. More recently, retiform purpura has been observed in patients presenting with the coronavirus disease of 2019 (COVID-19).

Levamisole is an immunomodulatory agent previously employed to treat autoimmune disorders and

malignancies. Its mechanism of action is thought to involve neutrophil stimulation and T-cell proliferation [1]. Due to adverse effects, most notably severe neutropenia, levamisole was banned from US markets in 1999. Since then, levamisole has gained recognition as an additive in cocaine. Aminorex, an active metabolite of levamisole, has a similar potency and mechanism of action to cocaine [2, 3]. Levamisole's current use in veterinary medicine makes it widely accessible. Its physical properties make it virtually indistinguishable from cocaine. Levamisole is therefore able to potentiate the effects of cocaine while reducing costs to producers. According to the DEA, in 2009, approximately 71% of cocaine in the US was contaminated with levamisole, and by October 2017, that number had increased to 87% [3, 4].

## Literature review

The adverse effects of levamisole-contaminated cocaine were first reported in a case series of unexplained agranulocytosis in cocaine users in 2009 [5]. In 2011, the first cases of levamisole-induced retiform purpura were described [6]. Patients presented with a net-like, or retiform, purpura progressing to necrosis after exposure to

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levamisole-contaminated cocaine. In subsequent cases, patients presented with multiorgan involvement including acute kidney injury, alveolar hemorrhage, and pneumonia [7]. Since then, levamisole-contaminated cocaine has become a well-described cause of a vasculitis characterized by retiform purpura with or without end-organ involvement.

COVID-19 is a predominantly respiratory syndrome caused by the novel severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2). It was first reported from Wuhan, China in December 2019. By March 2020, it had been declared a pandemic by the World Health Organization (WHO) [8]. Manifestations of COVID-19 range from asymptomatic carriers, to respiratory disease, to multiorgan dysfunction and failure [9]. As the disease has progressed, the cardiac, gastrointestinal, renal, and neurologic manifestations of COVID-19 have been described [9].

More recently, COVID-19 has been linked to a variety of dermatologic manifestations [10, 11]. Suchonwanit et al. [12] categorized cutaneous lesions in COVID-19 into two major mechanistic patterns: (1) clinical features similar to viral exanthems, or (2) lesions secondary to systemic consequences of COVID-19, especially vasculitis and thrombotic vasculopathy. Within the category of thrombotic vasculopathy, retiform purpura has been described [13].

The overlap between the cutaneous and systemic symptoms of levamisole-induced and COVID-19-induced retiform purpura creates the potential for these two syndromes to mimic one another in clinical presentation. As the coronavirus pandemic progresses, the number of cases continues to rise [14]. At the same time, the unique psychosocial stressors created by the pandemic have the potential to increase rates of substance abuse among current users and the general population [15]. Not only is substance abuse a risk factor for contracting COVID-19, but it is also associated with greater morbidity and mortality due to the virus than is seen in the general population [16]. The resulting possibility that patients may present with one or both of these syndromes creates a diagnostic challenge with clinical implications.

This review of levamisole-induced and COVID-19-induced retiform purpura highlights their corresponding and distinctive features. Additionally, we propose a unique staging system for levamisole-induced retiform purpura that may be valid for future classification of COVID-19-induced retiform purpura.

## Epidemiology and clinical presentation of levamisole-induced retiform purpura

### Epidemiology

Cutaneous symptoms occur in 0.5–3% of those exposed to levamisole-contaminated cocaine and typically appear 1–4 days after use [17]. Lesions occur regardless of the route of cocaine administration and progress in a dose-dependent manner [17–19]. Incidence is higher in women and in individuals with HLA B27 genotype or preexisting rheumatic disease [17, 20]. The average age of onset is 42.7 years [17].

### Clinical presentation

The classic presentation is a net-like, violaceous patch (Fig. 1). Lesions are typically bilateral, symmetric, and painful. Upon continued exposure to levamisole, lesions may progress to ulcerating bullae, skin sloughing, and necrosis (Fig. 2). Skin necrosis may become so severe that underlying soft tissue and bone become exposed (Fig. 3) [17]. Though the pathognomonic site of involvement is the pinna of the ear, the most common sites of involvement in decreasing prevalence are the face and lower extremities, ears, upper extremities, and trunk [7]. Oropharyngeal mucosal patches may also occur [21].

Based on the severity of skin manifestations, we propose a unique staging system for levamisole-induced retiform purpura summarized in Table 1. Lesions in stage I do not



**Fig. 1** Stage I: violaceous maculopapular plaques, net-like/reticular pattern



**Fig. 2** Stage II: progression to bullae, ulceration, skin sloughing, and necrosis



**Fig. 3** Stage III: revelation of underlying fascia, tendon, adipose tissue, and muscle

always progress to more severe stages. It is common for such lesions to spontaneously resolve upon cessation of cocaine, and therefore levamisole. Upon repeat exposure, lesions tend to progress to more severe stages at increasing rates [21, 22].

In addition to cutaneous symptoms, arthralgias and constitutional symptoms are common. In one case series by McGrath et al. [23], 72% of patients reported at least one constitutional symptom including fever, night sweats, weight loss, or malaise, and 83% of patients reported arthralgias. In another case series by Munoz et al. [24], 23% of patients reported fever and 40% reported arthralgias.

In the largest systematic review to date, Dartheval et al. [7] reviewed 192 cases of levamisole-induced vasculitis. While 94.8% of symptomatic patients had cutaneous manifestations, 12.5 and 10.4% presented with acute kidney injury or pulmonary disease, respectively. Among patients with acute kidney injury, renal biopsy most commonly demonstrated crescentic glomerulonephritis. Of these patients, 41.7% recovered, and 29.2% went on to develop chronic renal insufficiency. Among patients with pulmonary involvement, alveolar hemorrhage and pneumonia were the most common presentations. One patient died of necrotizing pneumonia. In other case reports describing pulmonary involvement, patients presented with shortness of breath and imaging abnormalities. Chest X-ray demonstrated pulmonary infiltrates and chest computed tomography demonstrated ground-glass opacities [7, 23–26]. An overview of the systematic manifestations of levamisole-induced vasculitis is described in Table 2.

### Pathogenesis

Pathogenesis is thought to be due to a combination of direct toxicity to neutrophils and endothelial cells as well as the loss of tolerance to self-antigens leading to autoimmunity [32]. The mechanism by which these autoantibodies develop is not fully understood, but recent reports have implicated neutrophil extracellular traps (NETs) [27–29].

NETs are collections of mitochondrial DNA bound to neutrophil granule proteins such as neutrophil elastase and myeloperoxidase. Under normal conditions, NETs are released by neutrophils in response to bacterial infection or other physiologic stressors. Their high mitochondrial DNA content stimulates cytokine production for a regulated host-defense response [36].

Levamisole can directly induce the release of NETs from neutrophils via interaction with muscarinic receptors [34]. This excessive release of NETs causes neutrophil granule

**Table 1** Stages of levamisole-induced retiform purpura

Stage I	Retiform purpura: violaceous maculopapular plaques, net-like/reticular pattern
Stage II	Progression to bullae, ulceration, skin sloughing or necrosis
Stage III	Full-thickness necrosis, revelation of underlying soft tissue (e.g., fascia, tendon, adipose tissue, muscle) and/or bone

**Table 2** Systemic manifestations of levamisole-induced vasculitis

Renal	Necrotizing and crescentic pauci-immune glomerulonephritis, [1, 20, 27] membranous nephropathy, [1, 27, 28] interstitial nephritis [27]
Pulmonary	Alveolar hemorrhage, [20] pulmonary hypertension, [1] serositis [24]
Neurological	Multifocal inflammatory leukoencephalopathy, [29] seizures [24]
Musculoskeletal	Acute arthritis, chronic deforming seronegative arthritis [30]
Gastrointestinal	Acute pancreatitis, [31] hepatosplenomegaly [24]

contents to act as self-antigens. Processing by antigen-presenting cells leads to the formation of anti-neutrophil autoantibodies directed against granule contents (ANCA). ANCA then stimulate neutrophils, further promoting the release of NETs [33]. NETs released into vasculature cause direct toxicity to endothelial cells, impair vasorelaxation, and cause intravascular thrombosis [33, 34]. Binding of ANCA to NETs may trigger complement or Fc receptor-mediated inflammation, further contributing to their immunogenicity [35].

Understanding the molecular mechanism for the formation of NETs has implications for targeted therapies in the future. Recently, Sofoluwe et al. [37] demonstrated that ATP and the ATP channel pannexin1 (Panx1) contribute to NET formation. Panx1 KO mice and WT mice with Panx1 channel inhibition showed a reduction in NET production, making these potentially useful therapeutic targets for the future.

## Diagnosis

The presence of retiform purpura in the setting of cocaine use should raise high suspicion for levamisole exposure. An accurate drug history may be difficult to obtain, but the diagnosis may still be made in the context of negative cocaine and/or levamisole testing. Sensitivity for detecting cocaine via urine toxicology decreases 48 h after use [38]. Sensitivity for detecting serum or urine levamisole via liquid and gas chromatography–mass spectrometry diminishes 48–72 h after exposure [38].

The differential diagnosis for retiform purpura is broad and includes vasculitic, coagulopathic, viral, bacterial, autoimmune, and embolic etiologies as summarized in

Table 3. Infectious, coagulopathic, and embolic etiologies should be excluded first as they represent potential emergent situations [22].

Once the differential is narrowed and vasculitis is suspected, serologic studies for autoantibodies, especially ANCA, should be performed [22]. In patients presenting with skin lesions, 95–100% have positive ANCA serologies and of those over 90% demonstrate a p-ANCA predominant pattern [20, 25]. P-ANCA titers are exceptionally elevated compared to those seen in other vasculitides. Antibodies are generally directed against multiple, atypical antigens such as human neutrophil elastase (HNE), lactoferrin, and cathepsin G [20]. When present, p-ANCA antibodies directed against myeloperoxidase, its typical target, are found concomitantly with antibodies targeting multiple components of neutrophil granules. These findings are helpful in differentiating levamisole-induced vasculitis from other ANCA-associated vasculitides [1, 20]. Notably, the presence of p-ANCA directed against HNE is highly specific for levamisole-induced vasculitis [17]. When present, c-ANCA directed against proteinase antigen 3 appears at lower titers than in other vasculitides. The majority of patients are also positive for antiphospholipid antibodies including lupus anticoagulant and anticardiolipin [25, 44]. Positivity for antinuclear and anti-double-stranded DNA antibodies has been reported at varying frequencies [32].

Hematologic abnormalities occur in approximately 60% of patients with cutaneous symptoms [20]. Neutropenia and agranulocytosis are characteristic features, typically occurring 1–2 weeks after initial exposure [1]. Plasmacytoid lymphocytes in peripheral blood, bone marrow plasmacytosis, and megakaryocyte hyperplasia have been described

**Table 3** Differential diagnosis of retiform purpura [39, 40]

<b>Vasculitides:</b> granulomatosis with polyangiitis (Wegener's granulomatosis), polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome), [41] microscopic polyangiitis, cryoglobulinemia, erythema multiforme, levamisole-induced vasculitis
<b>Coagulopathies:</b> warfarin necrosis, heparin necrosis, purpura fulminans, immune thrombocytopenic purpura, disseminated intravascular coagulation
<b>Viral:</b> HIV, hepatitis B & C, HHV-8 Kaposi's sarcoma, [42] SARS-CoV-2 [13]
<b>Bacterial:</b> bacterial sepsis due to staphylococci, streptococci, vibrio, <i>M. morgani</i> , [43] ecthyma gangrenosum, acute meningococcemia, Rickettsial disease
<b>Vascular:</b> calciphylaxis
<b>Autoimmune:</b> toxic epidermal necrolysis, systemic lupus erythematosus, antiphospholipid syndrome
<b>Embolic:</b> septic, fat, air, cholesterol, marantic

in patients with agranulocytosis [1]. Other common findings include elevated erythrocyte sedimentation rate, elevated serum C-reactive protein, hypocomplementemia, elevated APTT and PT, and low protein C and S levels [17, 20, 32].

Histopathology of skin biopsy specimens typically reveals leukocytoclastic vasculitis and/or thrombotic vasculopathy in small-to-mid-sized vessels. Leukocytoclastic vasculitis may or may not be associated with fibrinoid necrosis [7, 17, 23]. Common findings include epidermal necrosis, dermal inflammation and hemorrhage, and thrombosis within dermal vessels [21]. Subepidermal edema, erythrocyte extravasation, and visualization of neutrophils in blood vessel walls have also been described [22]. Direct immunofluorescence has not been routinely performed, but in a series of 21 biopsies undergoing IF assay, 16 (76.2%) were positive for immunoglobulins and/or complement deposition [7].

### Treatment and prognosis

In the majority of cases, cessation of cocaine and therefore levamisole results in rapid improvement of cutaneous lesions within 2–3 weeks. Serological markers typically return to normal between 2 and 14 months, while neutrophil levels normalize after 5–10 days [17].

Continued use of cocaine is associated with progression of disease and poorer outcomes. Patients should be counseled on their cocaine use and advised that continued exposure or re-exposure could lead to more severe symptoms with faster onset in the future. Interventions to address patient substance-use disorders have led to improved short- and long-term outcomes for patients [45].

For symptomatic relief of pain, non-steroidal anti-inflammatory drugs including aspirin have been effective, especially in those with severe arthralgias [46]. Colchicine and oral antihistamines may also provide symptomatic relief [17].

For patients whose symptoms do not improve with cocaine cessation alone, and for those with systemic manifestations, oral steroids and other immunosuppressants may be effective [46]. Though systemic steroids have been routinely employed in all patients, their effect is unclear outside of systemic involvement or refractory cases [47]. Steroids should be used with caution due to the potential for adverse effects and immunosuppression, especially in patients with severe neutropenia. In cases of severe systemic involvement, dapsone, pentoxifylline, intravenous immunoglobulin, plasmapheresis, mycophenolate mofetil, cyclosporine, and other immunosuppressants have been utilized, although their efficacy is unclear [17]. Rituximab, though frequently used in the management of other ANCA-associated vasculitis, has been rarely used in the treatment of levamisole-induced

vasculitis. This may be due to the fact that it is recognized for causing a drug-induced cutaneous vasculitis itself. [48].

Patients with agranulocytosis or symptomatic neutropenia should be hospitalized and started on intravenous, broad-spectrum antibiotics. Granulocyte colony-stimulating factor may be considered for these patients if there is evidence of infection or if patients suffer from comorbid immunosuppression, such as in HIV-positive patients [19].

Patients with stage III skin lesions may require hospitalization, as wound debridement, skin grafts, and amputation may be necessary. The decision of when to operate is based on clinical judgement. Mcevenue et al. [49] found that early excision in the setting of ongoing purpura was associated with disease progression involving greater total body surface areas, possibly due to the pro-inflammatory effects of surgery [49]. They recommend initial excision to be performed after lesions are fully demarcated. Initial debridement should include fascial excision to reduce the need for additional operations. Earlier excision may be appropriate in the setting of wound sepsis. Following excision, staged grafting has led to improved patient outcomes [49].

## Epidemiology and clinical diagnosis of COVID-19-induced retiform purpura

### Epidemiology

While the true incidence of cutaneous symptoms in COVID-19 patients is evolving, a study by Recalcati [50] found that number to be over 20%. A variety of dermatologic morphologies have been described, of which retiform purpura is among the most common [13]. In the largest case series of COVID-19-induced retiform purpura to date, Freeman et al. [13] found that the average presenting age was 66 and lesions were more common in males.

### Clinical presentation

COVID-19 patients presenting with retiform purpura are typically critically ill. In the case series by Freeman et al. [13], 100% of patients were hospitalized, 82% presented with ARDS, and 91% required a ventilator and/or ECMO. This is consistent with other case series [10, 51–53]. Lesions typically present after the initial onset of COVID-19 symptoms and most commonly involve the hands and feet [8, 13, 45, 52, 53]. Lesions tend to be painless, but have been described as progressing to painful ischemia and necrosis [13, 51]. As of yet, no staging system for COVID-19-induced retiform purpura has been described. We suggest the staging system we propose for levamisole-induced retiform purpura may be valid.

In addition to the pulmonary manifestations, patients with COVID-19-induced retiform purpura are also commonly present with fever, malaise, and arthralgias [13, 51]. The most common complications seen in these patients are thrombotic events, including stroke and pulmonary embolism, as well as acute kidney injury [13, 51–53].

Pathogenesis of COVID-19-induced retiform purpura is thought to be due to a pauci-inflammatory thrombogenic vasculopathy seen exclusively in critically ill patients. Magro et al. [52] attributed the thrombogenic vasculopathy to a blunted type 1 interferon response, which is needed for viral elimination. Depressed interferon signaling leads to extensive viral replication and viral protein release. Viral proteins are then thought to localize to vascular endothelial cells, leading to activation of the mannan-binding lectin and alternative complement pathways. Complement activation and deposition leads to extensive vascular injury and thrombosis [52].

## Diagnosis

The differential diagnosis for COVID-19-induced retiform purpura includes other etiologies of retiform purpura, as summarized in Table 3.

For symptomatic patients in whom suspicion for COVID-19 exists, the Infectious Diseases Society of America (IDSA) recommends direct SARS-CoV-2 nucleic acid amplification testing of nasal specimens. Repeat testing following negative results is warranted when clinical suspicion remains high [54].

Histopathology of skin biopsy specimens consistently shows pauci-inflammatory thrombogenic vasculopathy with or without complement deposition in capillaries, venules, and arteries [11, 13, 51–53]. Patients often have an elevated D dimer level, suggesting an underlying prothrombotic state [51–53]. Normal-to-elevated fibrinogen, normal haptoglobin, and an absence of thrombocytopenia or schistocytes have been used to rule out DIC or thrombotic microangiopathy which has also been described in critically ill COVID-19 patients [10, 51, 53, 55].

## Treatment and prognosis of COVID-19-induced retiform purpura

Patients with COVID-19-induced retiform purpura are typically ill with a poor prognosis. Mortality ranges between 10 and 50% [13, 52, 53, 56]. While effective treatment for COVID-19 continues to evolve, the use of anticoagulants in those presenting with retiform purpura has shown some success [11]. In several cases, despite starting a prophylactic dose of anticoagulation at presentation, patients later

required therapeutic doses due to ongoing thrombosis [11]. In at least one case, anticoagulation was continued weeks after hospital discharge, with progressive resolution of cutaneous lesions [51].

Other treatment modalities commonly employed in severe COVID-19 such as antimalarials, antivirals, antibiotics, IL-6 inhibitors, and corticosteroids have been used at varying frequencies [13, 51, 56]. As of yet, no data comparing their relative effectiveness in treating COVID-19-induced retiform purpura have been published to our knowledge.

Severe COVID-19 has been linked to two scenarios: (1) a delayed induction of beneficial cytokines, especially type 1 interferons and (2) an overabundance of detrimental cytokines such as IL-6, otherwise known as the “cytokine storm” [57]. As previously discussed, COVID-19-induced retiform purpura appears to result from an inadequate type 1 interferon response. Therefore, immunosuppressants such as IL-6 inhibitors and corticosteroids, which are predominantly used in the context of cytokine storm, should be used with caution, if at all [57, 58]. Furthermore, IL-6 inhibitor antibodies have been linked to delayed thrombus resolution, further suggesting a limited role in the treatment of COVID-19-induced retiform purpura [59]. The administration of type I interferon as an effective therapeutic agent in severe COVID-19 is currently being explored in multiple clinical trials [57]. Currently, the NIH COVID-19 Treatment Guidelines Panel recommends against the use of interferons in severe COVID-19, except within ongoing clinical trials [60]. Additional well-designed studies evaluating the use of interferons in those with COVID-19-induced retiform purpura are anticipated.

A comparison of the clinical features of COVID-19-induced retiform purpura and levamisole-induced vasculitis is summarized in Table 4.

## Conclusions

Levamisole-induced and COVID-19-induced retiform purpura are two syndromes with overlapping clinical features. Accurate distinction between the two has significant clinical implications. Whereas one syndrome is primarily an autoimmune disease treated with immunosuppression, the other results from an inadequate immune response and is treated with anticoagulation. At the present time, the possibility that patients may present with one or both syndromes creates a diagnostic challenge. As the pandemic progresses, cases of COVID-19 continue to abound. At the same time, new psychosocial stressors produced by the pandemic are expected to increase rates of substance abuse. For a patient with retiform purpura

**Table 4** Clinical comparison of levamisole-induced and COVID-19-induced retiform purpura

	Levamisole-induced retiform purpura	COVID-19-induced retiform purpura
Epidemiology	F > M Average age 42.7	M > F Average age 66
Presentation	Cutaneous: retiform purpura (typically painful) Constitutional: fever, night sweats, weight loss, malaise Pulmonary: alveolar hemorrhage, pneumonia Renal: acute kidney injury MSK: arthralgias	Cutaneous: retiform purpura (typically painless) Constitutional: fever, malaise, Pulmonary: cough, shortness of breath, ARDS Renal: acute kidney injury MSK: arthralgias Hematologic: thrombotic events (stroke, PE)
Histopathology	Leukocytoclastic vasculitis ± fibrinoid necrosis Thrombotic vasculopathy	Pauci-inflammatory thrombogenic vasculopathy ± complement deposition
Laboratory findings	± cocaine/levamisole testing ANCA+ Neutropenia/agranulocytosis	+ SARS-CoV-2 testing Elevated d dimer, elevated acute phase reactants
Treatment	Cocaine cessation NSAIDs Steroids Immunosuppressants Surgical excision, grafting, amputation	Anticoagulation
Prognosis	Mortality low	Mortality high

and respiratory symptoms, testing for SARS-CoV-2 and screening for cocaine and/or levamisole may be helpful, but are not absolute. A patient with levamisole-induced vasculitis may incidentally test positive for COVID-19, and, conversely, a patient with COVID-19-induced retiform purpura may also use cocaine. An accurate diagnosis may rely on the clinical clues and distinguishing features outlined delineated herein.

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