# Infection-Triggered Presumed Isolated Necrotizing Digital Vasculitis Presenting as Systemic Vasculitis

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Systemic necrotizing vasculitides are life-threatening disorders that require prompt immunosuppressive therapy. However, a broad spectrum of infectious diseases can closely mimic systemic vasculitis, presenting with cutaneous small- or medium-vessel involvement and digital necrosis.[1,2] Distinguishing primary immune-mediated vasculitis from infection-driven vasculitis is crucial, as inappropriate immunosuppression in unrecognized infections may worsen outcomes.[3] We report a case of a child with infection-triggered presumed isolated digital necrotizing vasculitis, initially raising concern for systemic vasculitis.

A previously healthy 9-year-old boy presented to the pediatric emergency department with a 5-day history of fever up to 38 °C and bilateral swelling of the feet. Initial evaluation by orthopedics revealed no musculoskeletal pathology. Empirical oral amoxicillin–clavulanate was started. Despite treatment, the patient returned with progressive discoloration of the digits of both feet and the left hand (Figure 1). The parents had a second-degree consanguineous marriage, but there was no known family history of autoimmune or thrombotic disorders. On physical examination, a 2/6 systolic ejection murmur was audible. Gangrenous discoloration involved the digits of the left hand, left foot, and right foot, while all peripheral pulses were palpable bilaterally. The remainder of the systemic examination was unremarkable.

Initial laboratory tests showed neutrophilic leukocytosis and elevated acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate). Other hematologic and biochemical parameters were within normal limits. Transthoracic echocardiography was unremarkable. Computed tomography (CT) angiography of the upper and lower extremities and chest CT revealed no vascular occlusion or structural abnormalities (Table 1). Upon admission, empirical broad-spectrum antimicrobial therapy (ceftriaxone, clindamycin, teicoplanin, and fluconazole) was initiated for presumed septic emboli. On day 7, blood cultures grew *Cryptococcus neoformans*, prompting escalation to amphotericin B. Ceftriaxone was discontinued on day 14, and clindamycin and teicoplanin were discontinued on day 21.

After discontinuation of clindamycin and teicoplanin (while receiving amphotericin B on day 15 of treatment), the patient developed persistent fever, and repeat blood cultures yielded Serratia marcescens. Meropenem was started, resulting in rapid clinical improvement. Amphotericin B was discontinued on day 21, and meropenem was stopped after 14 days.

Cardiovascular surgery recommended iloprost, a synthetic prostacyclin analog, as a vasodilator. Topical nitroglycerin patches were applied locally, and the patient received 20 sessions of hyperbaric oxygen therapy during hospitalization. Iloprost was discontinued on day 10, and nitroglycerin patches were stopped on day 7.

At the time of treatment initiation, the clinical course and underlying pathophysiology were uncertain, and a chronic inflammatory vasculopathy could not be excluded. Due to concern for systemic vasculitis, high-dose intravenous methylprednisolone (2mg/kg/day) and a single dose of intravenous immunoglobulin (1 g/kg) were administered to attenuate immune-mediated vascular inflammation and limit microvascular ischemic injury, while broad-spectrum antimicrobial therapy continued to ensure infection control. Azathioprine (2.5 mg/kg/day) was subsequently introduced as a steroid-sparing immunosuppressant to address presumed ongoing vasculitic activity, mitigate the risk of disease progression or relapse, and maintain sustained disease control.

Anticoagulation with enoxaparin was continued until day 14 of hospitalization, after which antithrombotic therapy was deescalated to acetylsalicylic acid, maintained until antiphospholipid antibody syndrome (APS) and an underlying arterial thrombotic disorder were excluded. Nifedipine (0.3 mg/kg/day), a dihydropyridine calcium channel blocker, was initiated as a targeted vasodilator therapy to promote peripheral arterial dilation and improve digital perfusion in the context of severe digital ischemia and evolving necrosis.

Serologic evaluation for vasculitis and autoimmune disease was negative for antinuclear antibody, anti–double-stranded DNA antibody, cytoplasmic anti–neutrophil cytoplasmic antibody (cANCA), perinuclear ANCA, and antiphospholipid antibodies. Serum

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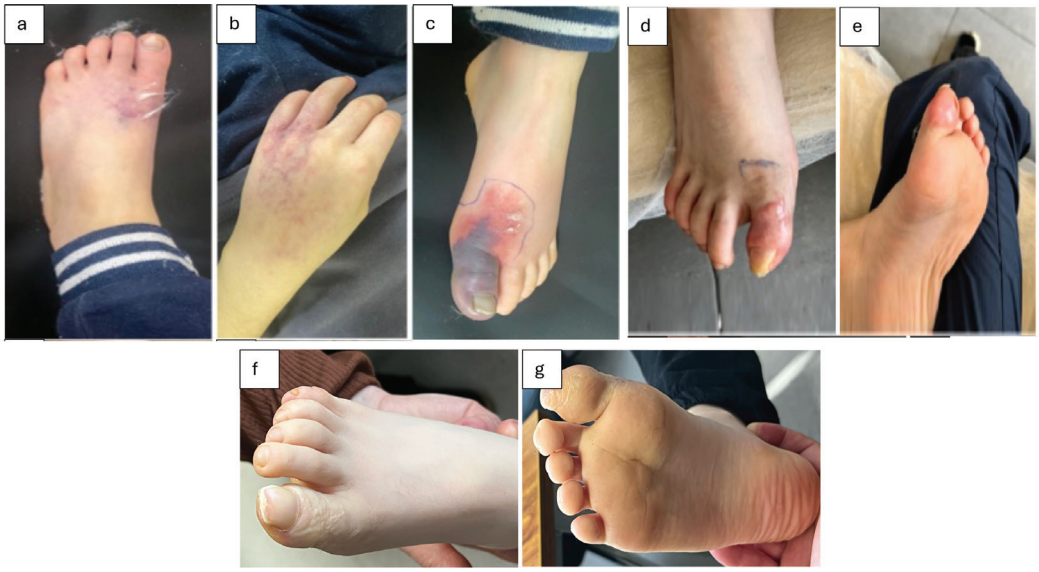


**FIG. 1.** Images illustrating digital necrosis at the time of hospital admission and prior to discharge. (a-c) Necrotic discoloration of the left foot, left hand, and right foot at presentation (d, e) improved appearance of the right foot prior to discharge. (f, g) Appearance of the right foot at the three-year final follow-up visit.

adenosine deaminase 2 (ADA2) activity was within the normal range, and genetic testing for ADA deficiency (DADA2) identified no pathogenic variants. Cardiac biomarkers were unremarkable. Coagulation studies showed normal international normalized ratio and activated partial thromboplastin time, decreased fibrinogen levels, and markedly elevated D-dimer concentrations (Table 1). A comprehensive immunological assessment, including quantitative immunoglobulin levels, lymphocyte subset analysis, and complement studies, revealed no evidence of underlying immunodeficiency.

The patient was hospitalized for 36 days. During follow-up, the necrotic appearance of the digital lesions gradually improved (Figure 1). Systemic corticosteroid therapy was progressively tapered and discontinued before discharge. The patient did not require amputation, and follow-up blood cultures remained negative. He was discharged on acetylsalicylic acid, azathioprine, and nifedipine.

During outpatient follow-up in the pediatric rheumatology clinic, the patient remained asymptomatic, and all laboratory investigations, including genetic testing for hereditary thrombophilia, were normal. Consequently, azathioprine, acetylsalicylic acid, and nifedipine were discontinued at the 6-month follow-up visit, at which time the patient remained clinically stable, laboratory findings had normalized, and no evidence of chronic disease was identified. He has since been followed for 3 years without recurrence of symptoms and remains off all immunosuppressive therapy. The absence of relapse during this period supports the interpretation of a monophasic, infection-triggered vasculitic event rather than chronic systemic vasculitis.

In children, digital necrotizing vasculitis is an uncommon but high-morbidity presentation that requires a broad, pediatric rheumatology–oriented differential diagnosis. Relevant considerations include medium- and small-vessel vasculitides (polyarteritis nodosa, ANCA-associated vasculitis, and immune complex–mediated vasculitides), monogenic vasculopathies such as DADA2 and type I interferonopathies (e.g., stimulator of interferon genes-associated vasculopathy), connective tissue diseases (systemic lupus erythematosus, juvenile dermatomyositis, juvenile systemic sclerosis), and secondary autoimmune or thrombotic conditions, particularly APS and cryoglobulinemia.[4-9] Given the substantial overlap in clinical and laboratory features, careful exclusion of cardiac embolic sources and infection-related vascular injury is essential in all children presenting with digital necrosis.

Septic embolism was initially considered but deemed unlikely. Peripheral pulses were bilaterally preserved, transthoracic echocardiography revealed no vegetations or intracardiac thrombi, and CT angiography of all extremities demonstrated patent vessels without embolic occlusion. Moreover, ischemic and necrotic lesions were bilateral, symmetric, and involved multiple digits of both feet and the left hand, a distribution contrasting with the typically focal, asymmetric, territory-dependent pattern of septic emboli. Although CT angiography cannot fully exclude microembolic phenomena, the absence of macroscopic emboli, combined with a normal cardiac workup, preserved distal pulses, and diffuse symmetric involvement, renders septic embolism an unlikely primary mechanism.

Severe soft tissue infection with secondary tissue hypoxia was also carefully evaluated. Imaging did not demonstrate necrotizing soft tissue infection, abscess formation, or compartment syndrome. The necrotic lesions closely followed the vascular territories of the affected digital arteries, rather than a pattern originating in the soft tissues and secondarily involving the vasculature (Figures 1a and b). Taken together, the vascular-territory–congruent distribution of necrosis, radiographic exclusion of deep soft tissue infection, and clinical response to vasodilatory, antimicrobial, and immunomodulatory therapy strongly support a primary vascular process and argue against isolated infectious tissue necrosis as the dominant mechanism.

**TABLE 1.** Laboratory Imaging and Treatment Approaches in the Present Case.

| Laboratory investigation | Imaging | Serological markers | Treatment |
|---|---|---|---|
| **Hemoglobin:** 11.2 g/dL<br>**White blood cell:** 20.600/mm$^3$<br>**Platelet count:** 291.000/mm$^3$<br>**Urea:** 9 mg/dL<br>**Serum creatinine:** 0.51 mg/dL<br>**AST:** 44 IU/L<br>**ALT:**13 IU/L<br>**CRP:** 21.1 mg/L<br>**ESR:** 42 mm/h<br>**PT:** 14.4 s<br>**aPTT:** 29.3 s<br>**INR:** 1.24<br>**Fibrinogen:** 91.6 mg/dL<br>**D-dimer:** 35.2 mg/L<br>**Direct Coombs test:** Negative<br>**Cardiac biomarkers:** Negative | **Echocardiography:** Normal<br>**CT angiography (upper and lower extremities):** Normal<br>**Thoracic CT:** Normal | **ANA:** Negative<br>**Anti-dsDNA:** Negative<br>**cANCA:** Negative<br>**pANCA:** Negative<br>**Antiphospholipid antibody IgM/G:** Negative<br>**Serum ADA2 level:** Normal<br>**Autoinflammatory panel:** Normal (no significant variant in DADA2) | **From a pediatric rheumatology perspective:**<br>• Methylprednisolone<br>• IVIG<br>• Nifedipine<br>• Azathioprine<br>• Enoxaparin switched to acetylsalicylic acid<br>**From an infectious disease perspective:**<br>• Ceftriaxone<br>• Clindamycin<br>• Piperacillin/tazobactam<br>• Fluconazole switched to Amphotericin B<br>• Meropenem<br>**From a cardiovascular surgery perspective:**<br>• Iloprost<br>• Topical nitroglycerin patches<br>• Hyperbaric oxygen therapy (20 sessions) |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; ADA2, adenosine deaminase 2; DADA2, ADA deficiency; CT, computed tomography; IVIG, intravenous immunoglobulin.

In this case, preserved peripheral pulses, normal vascular imaging, negative autoimmune serology, normal ADA2 activity, exclusion of autoimmune and hereditary thrombotic disorders, elevated inflammatory markers, documented *Serratia marcescens* bacteremia, and a robust response to combined antimicrobial and immunomodulatory therapy strongly support infection-triggered, presumed isolated digital vasculitis rather than a primary systemic or monogenic inflammatory disorder. Definitive histopathological confirmation was not possible, as tissue biopsy was infeasible, and vascular imaging did not reveal characteristic vessel wall inflammation or structural abnormalities—limitations well recognized in small-vessel vasculitis. Consequently, a definitive vasculitis diagnosis was avoided, and the term "infection-triggered, presumed isolated necrotizing digital vasculitis" was adopted, grounded in a characteristic clinical pattern and systematic exclusion of plausible mimics. The temporal association between cessation of antibacterial therapy, subsequent clinical deterioration, and rapid improvement after meropenem strongly implicates *Serratia marcescens* as the primary infectious trigger. In contrast, the patient's course argues against cryptococcal infection as a significant contributor to vascular injury. Gram-negative pathogens, including *Serratia marcescens*, are known to induce sepsis-associated acral ischemia and necrosis through endothelial damage and coagulation dysregulation, often mimicking primary vasculitic processes.[10,11]

Given the rapid progression and severity of digital necrosis, management was initiated urgently through a coordinated, multidisciplinary approach involving pediatric rheumatology, infectious diseases, and cardiovascular surgery. Interventions were applied simultaneously with the diagnostic workup and continued until infection-triggered etiology was confirmed and systemic vasculitic or monogenic causes were confidently excluded. These observations highlight the critical role of early microbiological evaluation, meticulous exclusion of vasculitis mimics, and prompt, multidisciplinary intervention to prevent unnecessary prolonged immunosuppression while enabling timely, pathogen-directed therapy.

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