

# Penicillin-induced Cutaneous Necrotizing Eosinophilic Vasculitis with Cryofibrinogenemia

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**ABSTRACT** Cutaneous necrotizing eosinophilic vasculitis (CNEV) is a rare type of vasculitis. Eosinophilic vasculitis is a necrotizing vasculitis with eosinophilic vascular infiltration, in which eosinophils mediate vascular damage in the disease process. We present a case of an 18-year-old girl who developed palpable purpura and hemorrhagic bullae over the lower extremities associated with itching, 7 days after the commencement of penicillin therapy. Plasma cryofibrinogen was positive. Histopathology showed an infiltration of eosinophils within and around the vessel walls and a complete absence of nuclear dust and neutrophils. Oral prednisone at 1 mg/kg induced remission in 2 weeks; the prednisone dose was tapered and discontinued after 2.5 months. There was no evidence of recurrence after 37 months of follow-up. Our patient represents a rare case of drug/penicillin-induced CNEV associated with cryofibrinogenemia, without systemic organ involvement.

**KEY WORDS:** cutaneous necrotizing eosinophilic vasculitis, drug-induced, penicillin, cryofibrinogenemia

## INTRODUCTION

Eosinophilic vasculitis is a rare type of vasculitis in patients without marked hypereosinophilia or systemic symptoms, with histological finding of small-vessel necrotizing vasculitis (1). Eosinophilic vasculitis may be an idiopathic or primary process (2) that overlaps with hypereosinophilic syndrome (HES), without specific immunoserological findings (1), or secondary to connective tissue diseases (CTD) (3), parasitic infections, or eosinophilic granulomatosis with polyangiitis (EGPA) (4).

We present a rare case of drug-induced cutaneous necrotizing eosinophilic vasculitis (CNEV), an unusual form of drug eruption triggered by penicillin, associated with cryofibrinogenemia, without systemic organ involvement.

## CASE REPORT

An 18-year-old girl had been treated with intramuscular penicillin because of tonsillopharyngitis and fever. Purpuric lesions appeared on her legs on

the 7<sup>th</sup> day of penicillin treatment. Large, tense hemorrhagic bullae developed within a few days. The patient reported moderate itching during the development of new lesions. There was no fever, joint pain, or headache. There was no nausea, vomiting, hematuria, or urinary symptoms. The patient had no history of allergic diseases such as asthma or allergic rhinitis.

Physical examination showed disseminated palpable purpura and hemorrhagic bullae, 5 to 20 mm in diameter, over the legs (Figure 1). Some lesions were arranged in a linear pattern (Koebner's phenomenon) (Figure 2). The lower extremities were slightly edematous.

Erythrocyte sedimentation rate and C-reactive protein were 26 mm/h and 22 mg/L (normal <5

mg/L), respectively. Complete blood count with differential was normal, except eosinophilia of 12.7% (absolute eosinophil count 952/mm<sup>3</sup>). Plasma cryofibrinogen was positive (++) . Serum routine biochemistry was normal. Blood coagulation tests, C3, C4, immunoglobulin levels (IgG, IgA, IgM), cryoglobulins, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, and anti-streptolysin-O were normal or negative. Serology tests for hepatitis B, C and Epstein-Barr virus were negative. Serum protein electrophoresis was normal, and there was no evidence of monoclonal gammopathy. Chest X-ray examination and abdominal ultrasonography were normal. The patient did not have any symptoms or signs of CTD or internal organ involvement.

**Table 1.** Reported cases of primary recurrent cutaneous necrotizing eosinophilic vasculitis

Case	Age/ Sex	Skin lesions	Peripheral eosinophilia	Immunology	Other abnormalities	Treatment
Chen, 1994 (5)	56/F	erythematous papules, purpuric papules, urticarial plaques, angioedema	1.4×10 <sup>9</sup> /L	normal	gingivitis	prednisone, hydroxyurea
Chen, 1994 (5)	18/F	erythematous papules, purpuric papules, urticarial plaques, angioedema	3.6×10 <sup>9</sup> /L	IgE 218 µg/L	hepatic vein occlusion, gingivitis	prednisone
Chen, 1994 (5)	17/M	erythematous papules, purpuric papules, urticarial plaques, angioedema	6.2×10 <sup>9</sup> /L	IgE 59.280 µg/L	transient lymphadenopathy with hepatosplenomegaly and total alopecia	topical corticosteroid, oral antihistamines
Launay, 2000 (6)	81/F	purpura with necrotic lesions	3.9×10 <sup>9</sup> /L	slightly positive ANA	no	prednisone
Sakuma-Oyama, 2003 (7)	27/F	palpable purpura, urticarial plaques, angioedema	14.4×10 <sup>9</sup> /L	ANA 1:320	no	prednisone, betamethasone with suplatast tosilate
Tsunemi, 2005 (8)	53/F	annular urticarial plaques	normal	normal	no	prednisone, betamethasone
Tanglertsampan, 2007 (9)	53/M	papules, nodules, and ulcers	normal	normal	no	prednisone, indomethacin
Kiorpelidou, 2011 (10)	82/F	polycyclic-annular, erythematous plaques and papules	normal	normal	chronic periaortitis	methylprednisolone, colchicine
Li, 2013 (2)	57/M	papules, purpuric plaques, necrotic lesions, angioedema	3.4×10 <sup>9</sup> /L	IgE 658.3 IU/mL	no	prednisone, glycyrrhizin
Sugiyama, 2013	80/F	multiple purpuric patches	10.080/µL	normal	no	prednisone, oral tacrolimus
Sawada, 2016 (11)	55/F	erythemas	781/µL	normal	Budd-Chiari syndrome	balloon angioplasty and warfarin for hepatic veins, systemic corticosteroid
Riyaz, 2016 (12)	45/F	multiple, discrete, and confluent purpuric papules and plaques, angioedema	normal	normal	no	prednisone

The histological finding (purpuric lesion on the right lower leg) showed an infiltration of eosinophils within and around the walls of arterioles and venules in the dermal superficial vascular plexus (Figure 3), and a complete absence of neutrophils and nuclear dust. Fibrin deposits in the vessel walls, luminal occlusions of the vessels (Figure 4), and extravasation of red blood cells were also present. Direct immunofluorescence was negative.

The patient was initially treated with oral prednisone at 1 mg/kg/day with gradual dose tapering over 2.5 months. After 9 weeks, the lesions cleared completely with residual hyperpigmentation and scarring; cryofibrinogen was negative. The patient has not experienced any recurrence after 37 months of follow-up. Penicillin avoidance was recommended.

## DISCUSSION

Eosinophilic vasculitis, an idiopathic disease commonly known as recurrent CNEV, is a rare entity first described in 1994. Recurrent CNEV is clinically characterized by recurrent, multiple, pruritic skin lesions with a chronic/relapsing course and by the absence of any features of systemic disease or specific immunoserological findings. To the best of our knowledge, only 12 patients with RCNEV have been described in the literature (Table 1) (2,5-12). Patients with recurrent CNEV usually have peripheral blood eosinophilia, but the eosinophil count does not always parallel the severity of the disease and some patients experience cutaneous eruption without peripheral blood eosinophilia. Systemic corticosteroids were effective in all cases; however, recurrences were common after treatment cessation (2,5).

HES encompasses a wide range of clinical manifestations sharing 3 features: 1) peripheral eosinophilia  $>1500/\text{mm}^3$  on at least 2 occasions; 2) evidence of organ involvement; 3) absence of other causes of



**Figure 1.** Palpable purpura and hemorrhagic bullae on both lower extremities (with marked skin discoloration caused by eosin).

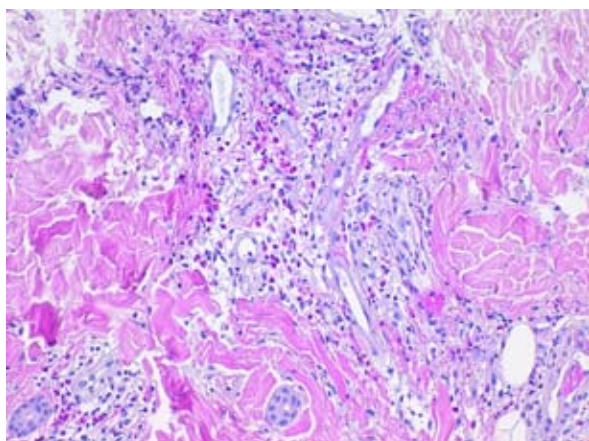
eosinophilia (parasite infection/infestation, atopic and/or allergic diseases, adverse drug reaction, hypoadrenalism, neoplasms, collagen-vascular disease) (13). However, eosinophilic vasculitis in HES is rare: only 8 cases have been reported so far (14). EGPA usually presents in three phases: the prodromal phase characterized by asthma with or without allergic rhinitis; the eosinophilic phase characterized by blood and tissue eosinophilia; and the vasculitic phase. Eosinophilic vasculitis has rarely been described in cutaneous vasculitic lesions of EGPA (4). Since our patient had mild eosinophilia and there was no evidence of visceral involvement, she did not fulfill the criteria for either HES or EGPA.

Eosinophilic vasculitis is very rarely associated with CTDs. This group of patients usually presents with pruritic, erythematous, or purpuric papules with peripheral blood eosinophilia and hypocomplementemia, and, generally, responds to corticosteroids (3). Our patient fulfilled no criteria for CTDs.

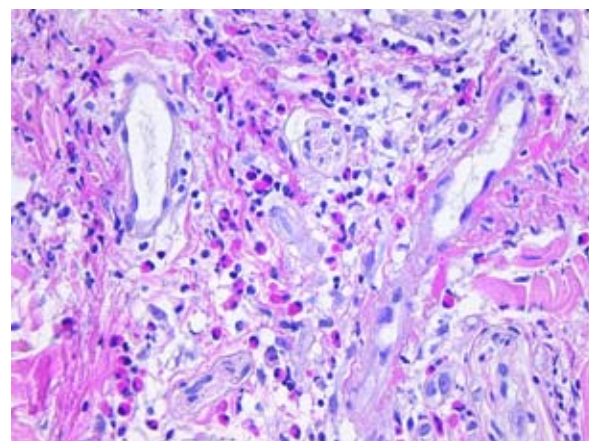
Based on histology, vasculitis can be classified according to the size of vessels affected and the dominant cells mediating the inflammation (neutrophilic, granulomatous, lymphocytic, or eosinophilic) (15). Histologically, eosinophilic vasculitis is a term for necrotizing vasculitis with eosinophilic vascular infiltration without leukocytoclasia (5). Eosinophilic leukocytoclastic vasculitis presents with palpable purpura, indistinguishable from classic leukocytoclastic vasculitis (LCV). It can be caused by infections, drugs, or other triggers, similar to classic LCV. In eosinophilic LCV, histopathologically, predominant eosinophils are found together with neutrophils, lymphocytes, extravasated erythrocytes, nuclear dust, fibrin in and around vessel walls, as well as collagen degeneration (16). In our case, necrotizing vasculitis of dermal small vessels with prominent infiltration of eosinophils without neutrophils and leukocytoclasia strongly supported the diagnosis of CNEV. Clinically, eosinophilic vasculitis is usually accompanied by more or



**Figure 2.** Koebner's phenomenon.



**Figure 3.** Histopathological findings: infiltration of eosinophils and a few lymphocytes and histiocytes around and within the vessel walls, luminal occlusions of the vessels (hematoxylin and eosin,  $\times 200$ ).



**Figure 4.** Histopathological findings: infiltration of eosinophils and a few lymphocytes and histiocytes around the vessel walls, luminal occlusions of the vessels, complete absence of neutrophils and nuclear dust (hematoxylin and eosin,  $\times 400$ ).

less severe itch, while “classical” LCV is usually not pruritic (2,5).

Drug-induced LCV can also feature prominent blood eosinophilia and a high degree of tissue eosinophilia (17). In the classical drug-induced LCV limited to the skin, just the discontinuation of causative drug, bed rest, and topical corticosteroid therapy may be sufficient. Only severe cases may necessitate systemic corticosteroid therapy (18). On the other hand, systemic corticosteroids should be the first-line therapy in eosinophilic vasculitis for at least two reasons: a) to reduce blood and tissue eosinophilia, preventing eosinophil-mediated tissue damage; b) to prevent a potentially life-threatening prothrombotic state (19).

Cryofibrinogenemia may be essential or secondary to underlying disorders (malignancies, drugs, infection, vasculitis, CTDs, or associated with cryoglobulinemia) (20). In eosinophilic vasculitis, microthrombi are possibly induced by high levels of major basic protein released by numerous eosinophils. Major basic protein has direct toxic effects on microvascular endothelial cells, exposing collagen and thus causing clot formation (21). We did not detect cryofibrinogen deposition on serial sections of the biopsy performed on an early lesion, but we cannot exclude the possibility of later deposition of cryofibrinogen in previously damaged blood vessels subsequently producing more severe necrosis resulting in blister formation. It has been shown that cryofibrinogenemia may severely complicate (infection, sepsis) the course of underlying disease (20). Unfortunately, in many centers, cryofibrinogen is not always sought for.

## CONCLUSION

CNEV is a rare or underreported disease, while penicillin- or other drug-induced CNEV has never been reported before. Furthermore, the association of cryofibrinogenemia and CNEV has not been reported so far. New cases should be investigated to elucidate all the pathogenic processes active in this peculiar disease.

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