

# Erythema Nodosum Triggered by a Bite From a Copperhead Snake

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## PRACTICE POINTS

- Erythema nodosum (EN) can occur following snakebites from pit vipers such as the eastern copperhead.
- The acute phase of EN is neutrophilic and responds to colchicine. The chronic phase of EN is granulomatous and responds best to rest and elevation as well as nonsteroidal anti-inflammatory drugs and iodides.

Erythema nodosum (EN) is a form of septal panniculitis that can occur secondary to multiple etiologies including inflammatory disorders, infections, or medications. We describe a 42-year-old woman who developed tender, erythematous, subcutaneous nodules persisting for 4 months following a copperhead snakebite. The diagnosis of EN was confirmed via histopathology, and the patient was treated with colchicine. Physicians should be aware of possible etiologies of EN to evaluate patients who present with new-onset tender subcutaneous nodules. Additionally, physicians should understand the various complications that can result from snakebites, with the potential for lingering cutaneous manifestations weeks to months following the initial bite.

The clinical manifestations of snakebites vary based on the species of snake, bite location, and amount and strength of the venom injected. Locally acting toxins in snake venom predominantly consist of enzymes, such as phospholipase A<sub>2</sub>, that cause local tissue destruction and can result in pain, swelling, blistering, ecchymosis, and tissue necrosis at the site of the bite within hours to days after the bite.<sup>1</sup> Systemically acting toxins can target a wide variety of tissues and cause severe systemic complications including paralysis, rhabdomyolysis

secondary to muscle damage, coagulopathy, sepsis, and cardiorespiratory failure.<sup>2</sup>

Although pain and swelling following snakebites typically resolve by 1 month after envenomation, copperhead snakes—a type of pit viper—may cause residual symptoms of pain and swelling lasting for a year or more.<sup>3</sup> Additional cutaneous manifestations of copperhead snakebites include wound infections at the bite site, such as cellulitis and necrotizing fasciitis. More devastating complications that have been described following snake envenomation include tissue injury of an entire extremity and development of compartment syndrome, which requires urgent fasciotomy to prevent potential loss of the affected limb.<sup>4</sup>

Physicians should be aware of the potential complications of snakebites to properly manage and counsel their patients. We describe a 42-year-old woman with tender, erythematous, subcutaneous nodules persisting for 4 months following a copperhead snakebite. A biopsy confirmed the diagnosis of snakebite-associated erythema nodosum (EN).

## Case Report

A 42-year-old woman presented to our clinic with progressive tender, pruritic, deep-seated, erythematous nodules in multiple locations on the legs after sustaining a bite by a copperhead snake on the left foot 4 months prior. The lesions tended to fluctuate in intensity. In the days following the bite, she initially developed painful red bumps on the left foot just proximal to the bite site with associated pain and swelling extending up to just below the left knee. She reported no other notable symptoms such as fever, arthralgia, fatigue, or gastrointestinal tract symptoms. Physical examination revealed bilateral pitting edema, which was worse in the left leg, along with

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multiple deep, palpable, tender subcutaneous nodules with erythematous surface change (Figure 1).

Workup performed by an outside provider over the previous month included 2 venous duplex ultrasounds of the left leg, which showed no signs of deep vein thrombosis. Additionally, the patient underwent lateral and anteroposterior radiographs of the left foot, tibia, and fibula, which showed no evidence of fracture.

Given the morphology and distribution of the lesions (Figure 2), EN was strongly favored as the cause of the symptoms, and a biopsy confirmed the diagnosis. All immunohistochemical stains including auramine-rhodamine for acid-fast bacilli, Grocott-Gomori methenamine silver for fungal organisms, and Brown and Brenn were negative. Given the waxing and waning course of the lesions, which suggested an active neutrophilic rather than purely chronic granulomatous phase of EN, the patient was treated with colchicine 0.6 mg twice daily for 1 month.

### Causes of EN and Clinical Manifestations

Erythema nodosum is a common form of septal panniculitis that can be precipitated by inflammatory conditions, infection, or medications (commonly oral contraceptive pills) but often is idiopathic.<sup>5</sup> The acute phase is neutrophilic, with evolution over time to a granulomatous phase. Common etiologies include sarcoidosis; inflammatory bowel disease; and bacterial or fungal infections

such as *Streptococcus* (especially common in children), histoplasmosis, and coccidioidomycosis. The patient was otherwise healthy and was not taking any medications that are known triggers of EN. A PubMed search of articles indexed for MEDLINE in the English-language literature using the terms *copperhead snake bite*, *erythema nodosum snake*, and *copperhead snake erythema nodosum* revealed no reports of EN following a bite from a copperhead snake; however, in one case, an adder bite led to erysipelas, likely due to disturbed blood and lymphatic flow, which then triggered EN.<sup>6</sup> Additionally, EN has been reported as a delayed reaction to jellyfish stings.<sup>7</sup>

Clinical features of EN include the development of tender, erythematous, subcutaneous nodules and plaques most frequently over the pretibial region. Lesions typically evolve from raised, deep-seated nodules into flat indurated plaques over a span of weeks. Occasionally, there is a slight prodromal phase marked by nonspecific symptoms such as fever and arthralgia lasting for 3 to 6 days. Erythema nodosum typically results in spontaneous resolution after 4 to 8 weeks, and management involves treatment of any underlying condition with symptomatic care. Interestingly, our patient experienced persistent symptoms over the course of 4 months, with development of new nodular lesions throughout this time period. The most frequently used drugs for the management of symptomatic EN include nonsteroidal anti-inflammatory drugs, colchicine, and potassium iodide.<sup>8</sup> A characteristic histologic finding of the granulomatous phase is the Miescher radial granuloma, which is a septal collection of histiocytes surrounding a cleft.<sup>9</sup>



**FIGURE 1.** Multiple palpable, erythematous, subcutaneous nodules scattered on the right leg in a patient with erythema nodosum following a bite from a copperhead snake.



**FIGURE 2.** Punch biopsy site of an isolated erythematous plaque on the left upper thigh in a patient with erythema nodosum following a copperhead snake bite.

## Snakebite Reactions

Snakebites can result in a wide range of local and systemic manifestations, as snake venom may contain 20 or more toxins.<sup>10</sup> Local complications of pit viper bites include pain, swelling, and fang marks; when examining fang marks, the presence of 2 distinct puncture wounds often indicates envenomation with a poisonous snake, whereas nonvenomous snakebites often result in smaller puncture wounds arranged in an arc. Following bites, pain can develop immediately and spread proximally up the affected limb, which occurred in our patient in the days following the bite. Intense local reactions can occur, as bites often result in intense edema of the affected limb spreading to the trunk in the days to weeks after the bite, occasionally accompanied by regional lymphadenopathy. Some bites can result in local necrosis and secondary bacterial infection caused by organisms in the oral cavity of the culprit snake.

Although they were not present in our patient, snakebites can result in a wide range of systemic toxicities ranging from clotting defects and hemolysis to neurotoxicity, myotoxicity, and nephrotoxicity.<sup>10</sup> In severe cases, snake venom can result in disseminated intravascular coagulation, sepsis, and cardiorespiratory collapse.

The eastern copperhead (*Agkistrodon contortrix*) is a species of venomous snake that is endemic to eastern North America. Copperheads are members of the subfamily Crotalinae in the family Viperidae.<sup>11</sup> Reported reactions to copperhead bites include cellulitis, necrotizing fasciitis, compartment syndrome, and tissue necrosis of an entire affected extremity.<sup>12,13</sup> Our patient displayed no systemic symptoms to suggest envenomation.

## Management of Snakebites

Treatment of snakebites varies based on the constellation and severity of symptoms as well as how recently the envenomation occurred. In urgent cases, antivenom may be administered to prevent further toxicity. In cases of progressive compartment syndrome, emergent surgical procedures such as fasciotomy or amputation are required to prevent further complications. When a superimposed bacterial infection is suspected, broad-spectrum antibiotics are required. Because our patient presented 4 months following the initial bite with isolated cutaneous manifestations, she was treated symptomatically with colchicine for EN.<sup>1,2</sup>

## Final Thoughts

Our patient presented with EN following a bite from a copperhead snake. Physicians should be aware of possible etiologies of EN to evaluate patients who present with new-onset tender subcutaneous nodules. Additionally, physicians should be aware of venomous snakes endemic to their region and also understand the various complications that can result following a snakebite, with the potential for lingering cutaneous manifestations weeks to months following the initial bite.

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