

# Swelling and pain 2 weeks after a dog bite

A 48-YEAR-OLD MAN with gout, multiple sclerosis, and previously treated methicillin-resistant *Staphylococcus aureus* (MRSA) infection presented to the emergency room with pain and significant swelling at the site of a dog bite on his left forearm. He had been bitten 2 weeks earlier by a friend's dog, and the bite had punctured the skin. He also had red streaking on the skin of the left arm from the wrist to the elbow, and he reported feeling "feverish" and having night sweats.

At first, the bite had seemed to improve, then swelling and pain had developed and increased. He reported this to his primary care physician, along with the information that he had previously had an anaphylactic reaction to penicillin and a cephalosporin. His physician, considering a penicillin allergy, started him on ciprofloxacin (Cipro) plus clindamycin (Cleocin). The patient took this for 5 days, but without improvement. The appearance of the red streaking on his left forearm prompted his presentation to our emergency room.

## ■ ORGANISMS IN DOG BITES

1 Which is the most common cause of infected dog bite?

- Pasteurella canis*
- Streptococci and *S aureus*
- Erysipelothrix rhusiopathiae*
- Capnocytophaga canimorsus*
- Eikenella corrodens*

Streptococci (50%) and *S aureus* (20% to 40%) are the organisms most commonly responsible for infected dog bites, as they are for

other skin and soft-tissue infections.<sup>1</sup> *P canis* is unique to dog bite infections but accounts for only 18%.<sup>2</sup> *E rhusiopathiae* is an unusual isolate from cat and dog bites and is more commonly isolated from the mouths of fish and aquatic mammals. *C canimorsus* is a normal inhabitant of the oral cavity of dogs and cats but an unusual cause of wound infection from a dog bite. It is notable for sepsis and central nervous system infections uniquely associated with veterinarians, dog owners, kennel workers, and mail carriers.<sup>3</sup> *E corrodens* infection is more common with human bites.<sup>4</sup>

## ■ THE EVALUATION BEGINS

On examination, the patient had marked edema of the left forearm and pain in the joints of the left hand. His temperature was 100.2°F (37.9°C). Because of the duration and severity of symptoms, the examining physician was concerned about septic arthritis of the wrist, and the patient was admitted to the hospital.

In the hospital, our patient was thermodynamically stable without documented fever or chills. There was no open wound to culture, and blood cultures were negative. Marked edema and joint involvement raised suspicion of erysipelas. This "cousin" of erysipelas often involves the underlying joint, is associated with edema, and produces systemic manifestations of fever and arthralgia.

Radiography of the left forearm and hand demonstrated multiple foci of demineralization within the carpal bones and proximal radius, attributed to disuse. Magnetic resonance imaging (MRI) the next day showed multiple bone infarcts in the carpal bones and the distal radius, with synovitis and fluid in the carpal joints and without adjacent osteomyelitis. Fluid was

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also seen in the soft tissues in the ulnar aspect of the left wrist, and tenosynovitis involving the flexor carpi radialis tendon was noted.

Arthrocentesis of his left radiocarpal joint produced synovial fluid negative for crystals and negative on Gram stain; the fluid was also sent for culture. The patient's tetanus immunization was current, and the dog was known to have been immunized against rabies.

### ■ ANTIBIOTICS FOR INFECTED DOG BITES

**2** Which antibiotic regimen would you choose for this patient?

- Oral amoxicillin and clavulanate
- Meropenem
- Vancomycin, clindamycin, aztreonam
- Clindamycin and levofloxacin
- Clindamycin and trimethoprim-sulfamethoxazole

Oral amoxicillin and clavulanate (Augmentin) is a judicious choice for prophylactic treatment of deep bites in the early stages of infection. However, our patient's wound was no longer in the early stages of infection, and he had a history of an adverse reaction to penicillin.

Meropenem (Merrem IV) cross-reacts minimally with penicillin allergy and is reported to be safe in patients with a history of anaphylactic reactions to penicillin,<sup>5</sup> but overuse of carbapenems has led to the development of carbapenem-resistant strains of *Klebsiella*, *Stenotrophomonas*, and *Acinetobacter* organisms.

Given the rise of MRSA infections and the common involvement of staphylococci, streptococci, and anaerobic bacteria in complicated dog bites, the combination of vancomycin and clindamycin is a good choice, and aztreonam (Azactam) would add empiric coverage of gram-negative enteric organisms.

Levofloxacin (Levaquin) also covers gram-negative enteric organisms, but *Fusobacterium canifelinum*, a common anaerobe in the oral flora of dogs and cats, is intrinsically resistant to fluoroquinolones.

Clindamycin and levofloxacin would be a good step-down oral regimen. *Pasteurella multocida* has variable sensitivity to the commonly used agents dicloxacillin (Dynap-

en), cephalexin (Keflex), macrolides, and clindamycin, but it is a less likely pathogen at this late stage and could be covered with levofloxacin alone.

*C. canimorsus* is resistant to trimethoprim-sulfamethoxazole (Bactrim) and cephalexin, but is well covered by clindamycin.<sup>6</sup>

### ■ CASE CONTINUED

Our patient was started on intravenous vancomycin, clindamycin, and aztreonam for coverage of dog-mouth flora. Blood cultures and cultures of synovial fluid of the left wrist were negative. Vancomycin was discontinued after 48 hours when blood cultures did not grow staphylococcal organisms, but clindamycin and aztreonam were continued for a total of 8 days to treat possible infection with anaerobic and gram-negative enteric pathogens.

To test for autonomic dysfunction, a plastic pen case drawn lightly across each forearm revealed a loss of tactile adherence (ie, areas where moist, sweaty skin impeded the movement of the pen case) on the affected forearm, a sign of underlying nerve injury. The affected forearm was sensitive to light touch, with pain out of proportion to the stimulus.

### ■ ARRIVING AT THE DIAGNOSIS

Based on the wide distribution of inflammation, autonomic dysfunction (shown by differences in temperature and sweating), radiographic evidence of demineralization, hyperesthesia, and lack of improvement in pain and swelling after two courses of antibiotics, the patient's clinical course was determined to be consistent with complex regional pain syndrome type 1, previously referred to as reflex sympathetic dystrophy.

Symptoms of complex regional pain syndrome traditionally include pain, regional edema, joint stiffness, muscular atrophy, vasomotor disturbances (causing temperature variability and erythema), regional diaphoresis, and localized skeletal demineralization on radiography.

Complex regional pain syndrome type 1 occurs as regional pain and inflammation as an excessive sympathetic reaction to an often minor insult, without nerve injury. When the syndrome occurs in a patient with obvious

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TABLE 1

**The Budapest diagnostic criteria for complex regional pain syndrome**

Category	Criteria
<b>Sensory</b>	Hyperesthesia or allodynia
<b>Vasomotor</b>	Temperature asymmetry, skin-color changes, or skin-color asymmetry
<b>Sudomotor/edema</b>	Edema, sweating changes, or sweating asymmetry
<b>Motor/trophic</b>	Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), or trophic changes (hair, nails, skin)

The diagnosis requires at least one symptom (ie, reported by the patient) in three of the four categories and at least one sign (ie, observed at the time of evaluation) in two of the four categories in a patient with continuing pain disproportionate to an inciting event.

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partial nerve injury, it is categorized as type 2 (formerly known as causalgia). The two types are clinically indistinguishable and are not uncommon. About 10% of all patients with complex regional pain syndrome have obvious nerve injury (complex regional pain syndrome type 2). In a study of 109 patients with Colles fracture, 25% developed symptoms of complex regional pain syndrome.<sup>7</sup>

Complex regional pain syndrome is difficult to diagnose, as it resembles many other ailments, such as gout, infection, bone tumor, stress fracture, and arthritis. Its pathophysiology is poorly understood, but it is believed to result from a “short circuit” in the reflex arc between somatic afferent sensory fibers and autonomic sympathetic efferent fibers, and this is thought to explain the increased sympathetic stimulation.

Although the pathophysiology is likely the same in type 1 and type 2, electromyography with a nerve conduction study is a reliable way to detect nerve damage and thus distinguish between the two types of complex regional pain syndrome.<sup>8</sup>

Our understanding of this syndrome is evolving. A recent study using sensory testing showed that 33% of patients with type 1 had combinations of increased and decreased thresholds for the detection of thermal, vibratory, and mechanical stimuli in the distribution of discrete peripheral nerves, suggesting that the patients actually had type 2.<sup>9</sup>

### ■ CONFIRMING COMPLEX REGIONAL PAIN SYNDROME TYPE 1

**3** Which of the following is the best way to confirm complex regional pain syndrome type 1?

- Erythrocyte sedimentation rate, C-reactive protein, and complete blood cell count
- Plain radiography of the hand and forearm
- Three-phase technetium bone scan
- The Budapest diagnostic criteria
- MRI
- Autonomic testing

Complex regional pain syndrome type 1 is a clinical diagnosis. Diagnostic studies lack sensitivity and specificity but may confirm complex regional pain syndrome type 1 or rule out other diagnoses. The Budapest diagnostic criteria<sup>10</sup> (TABLE 1) may be the best way to confirm this diagnosis. The criteria are as follows: continuing pain disproportionate to an inciting event, coupled with three of four symptoms plus at least one sign from sensory, vasomotor, sudomotor, and motor-trophic categories.

Laboratory tests are not helpful because acute-phase reactants and blood counts remain normal in these patients.

Plain radiography is not sensitive in early diagnosis, but at 2 weeks it may show patchy areas of osteopenia in adjacent bones throughout the region, as well as subsequent diffuse demineralization.

**A multi-disciplinary approach is recommended at the outset**

Three-phase bone scanning is more sensitive than plain radiography, with 75% of patients showing regional disparities in blood flow in early sequences and increased bone uptake in the later sequences.

MRI is a sensitive early test, as it better defines focal areas of bone loss and increased T2 bone signal in adjacent bone, as well as early soft-tissue changes. Computed tomography does not show early specific changes in muscle, tendon, or bone and so is not recommended.

### ■ THE EVALUATION CONTINUES

The admitting diagnosis was septic arthritis, and our patient underwent computed tomography, which showed focal demineralization that could have represented bone infarcts or infection, confounding the diagnosis of complex regional pain syndrome.

Autonomic nerve testing can help distinguish complex regional pain syndrome from other disorders. Complex regional pain syndrome is characterized by increased sympathetic activity and results in increased sweat output. Autonomic testing includes resting sweat output, resting skin temperature, and quantitative sudomotor axon reflex testing. In one study, an increase in resting sweat output used in conjunction with quantitative sudomotor axon reflex testing predicted the diagnosis of complex regional pain syndrome with a specificity of 98%.<sup>11</sup> However, autonomic testing is limited to academic centers and is not readily available.

### ■ TREATING COMPLEX REGIONAL PAIN SYNDROME TYPE 1

**4** Which is the best first-line therapy for complex regional pain syndrome type 1?

- Stellate ganglion nerve block
- Occupational therapy to splint the wrist and forearm
- Oral corticosteroids
- Physical therapy to prevent loss of joint motion
- Tricyclic antidepressant drugs (eg, amitriptyline), pregabalin, and bisphosphonates

Physical therapy should be started early in all patients, with range-of-motion exercises to prevent contracture and enhance mobility.

Stellate ganglion nerve block has been used to counter severe sympathetic hyperactivity, but it also may aggravate symptoms of complex regional pain syndrome and so remains a controversial treatment.

Immobilization and splinting should be avoided, as this will augment edema, pain, and contracture of joints.

Corticosteroids do not shorten the course or assuage symptoms and may increase edema.

Amitriptyline (Elavil) and pregabalin (Lyrica) have been used successfully to counter extended courses of allodynia and hyperalgesia. Bisphosphonates may decrease bone loss and pain and may be needed should the course be complicated by myositis ossificans, a form of dystrophic bone formation in juxtaposed tendon and muscle related to neuroactivation of fibroblasts and osteoblasts.

### ■ THE COURSE OF COMPLEX REGIONAL PAIN SYNDROME

Traditionally, type 1 was divided into three stages—an early inflammatory stage, a dystrophic stage, and a late atrophic stage.<sup>12</sup> Although there is no evidence to support a consistent three-stage evolution, the severity of symptoms may help determine the best approach to management.<sup>13</sup>

Patients initially exhibit burning or throbbing pain, diffuse aching, sensitivity to touch or cold (allodynia), localized edema, and vasomotor disturbances of variable intensity that may produce altered color and temperature. Topical capsaicin cream; a tricyclic antidepressant; an anticonvulsant such as gabapentin (Neurontin), pregabalin, or lamotrigine (Lamictal); or a nonsteroidal anti-inflammatory drug should be tried first. Some of these treatments are poorly tolerated in elderly patients. If pain persists, nasal calcitonin may be added. Trigger-point injections with an anesthetic or glucocorticoid may be tried.

The management of early complex regional pain syndrome is sometimes supplemented with systemic corticosteroids, but reviews of randomized controlled trials have failed to show efficacy.<sup>14</sup>

Later in the course, patients may suffer persistent soft-tissue edema, accompanied by thickening of the skin and periarticular

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soft tissues, muscle wasting, and the skin changes of brawny edema. Regional blockade of sympathetic ganglions, epidural administration of clonidine, implantable peripheral nerve stimulators, and spinal cord stimulators have all been applied by experts in pain management and may provide benefit. Progression of the syndrome may include cyanosis, mottling, increased sweating, abnormal hair growth, and diffuse swelling in nonarticular tissue.

It is always acceptable to refer to an experienced pain management specialist, and a multidisciplinary approach is recommended at the outset.<sup>12</sup>

### ■ OUR PATIENT'S CARE CONTINUED

Our patient's forearm and wrist were placed in a sling to keep his left arm elevated when active. This helped control sympathetic vascular edema and throbbing pain. Physical therapy with range-of-motion exercises prevented contracture.

He was discharged home on limited oxycodone as needed, with close follow-up by his primary care physician to monitor his pain symptoms. The pain and swelling slowly improved over the next 2 months, but he suffered a fall, twisting his left wrist. This minor injury was followed by more intense pain and swelling of the forearm, hand, and wrist.

### ■ COMORBIDITIES

**5** Which of the following statements about conditions associated with complex regional pain syndrome most likely applies to our patient?

- Gout is likely following minor trauma
- Minor trauma or surgical bone biopsy may reactivate complex regional pain syndrome
- Septic hip arthritis due to MRSA may have reemerged and seeded the wrist
- Patients with multiple sclerosis have a propensity for complex regional pain syndrome
- Complex regional pain syndrome type 1 begets type 2

Gout does follow minor injury, but our patient's uric acid was well controlled on allo-

purinol (Zyloprim), and gout is unlikely to be causing polyarticular swelling of the hand, wrist, and forearm.

Minor trauma, sometimes inconsequential enough to have been completely forgotten, may either initiate complex regional pain syndrome or, as seen here, reactivate it. Bone changes seen on MRI sometimes trigger surgical bone biopsy, only to reactivate the dysesthesia and sympathetic vascular reaction. Surgery should be avoided. Trauma and surgery are causative rather than associative comorbidities.

Sepsis due to MRSA after total hip arthroplasty may be reactivated, especially in the setting of immunosuppressive treatment. But the diffuse bone changes seen in multiple carpal, radial, and ulnar bones suggest generalized vascular and sympathetic disarray, most consistent with complex regional pain syndrome type 1.

### ■ AN ASSOCIATION WITH MULTIPLE SCLEROSIS?

Multiple sclerosis and other central neuropathic conditions such as stroke are associated with complex regional pain syndrome type 1.<sup>15,16</sup>

A hypothetical cause for the higher prevalence of complex regional pain syndrome in patients with multiple sclerosis may be demyelination resulting in aberrant signaling and overreaction to distal pain receptors. Demyelination of neurons within the autonomic or spinothalamic tracts potentially increases susceptibility to development of the pain syndrome.

Our patient had an apparent stimulus for the development of the syndrome, ie, the initial dog bite, and the wrist injury later may have caused peripheral nerve injury. Such injury may lead to release of vasodilatory neuropeptides including substance P from stimulated cutaneous nerves with cell bodies in the dorsal root ganglia. Excessive vasodilation and increased vascular permeability result in the affected limb becoming edematous and causing cutaneous nerves to be further activated. Stimulated cutaneous neurons normally have an inhibitory influence on sympathetic activity at the level of entry of the dorsal root ganglia in the cord. In

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complex regional pain syndrome, this inhibition is lost, resulting in a hyperactive somatosympathetic reflex.<sup>17</sup> Underlying multiple sclerosis may have contributed to the loss of inhibition by the cutaneous nerves on the sympathetic system.

### ■ CASE CONCLUDED

We continued to closely follow this patient, who was on a self-directed program of physical therapy. One year after the original dog bite, the complex regional pain syndrome had completely resolved. ■

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