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Herpes Zoster

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Introduction

Background

Zoster is a common, predominantly dermal, and neurologic disorder caused by the varicella-zoster virus (VZV), a virus morphologically and antigenically identical to the virus causing varicella (chickenpox). Difference in clinical manifestations between varicella and zoster apparently depends on the immune status of individual patients; those with no prior immunologic exposure to varicella virus, most commonly children, develop the clinical syndrome of varicella, while those with circulating varicella antibodies develop a localized recrudescence, zoster.

Zoster probably results most often from a failure of the immune system to contain latent varicella-zoster virus replication. Whether other factors such as radiation, physical trauma, certain medications, other infections, or stress also can trigger zoster has not been determined with certainty. Nor is it entirely clear why circulating varicella antibodies and cell-mediated immune mechanisms do not prevent recurrent overt disease, as is common with most other viral illnesses.

An inverse correlation appears to exist between the capacity of a host to mount a cellular immune response and the incidence of zoster. However, many patients with zoster apparently have normal immune systems. In these patients, zoster is postulated to occur when varicella-zoster virus antibody titers and cellular immunity drop to levels at which they no longer are completely effective in preventing viral invasion. Evidence for this hypothesis includes the observation that pediatricians, who presumably are reexposed to the varicella virus routinely and thus maintain high levels of immunity to varicella-zoster virus, seldom develop zoster.

Pathophysiology

Zoster most commonly manifests in 1 or more posterior spinal ganglia or cranial sensory ganglia, presumably because viral particles have been preserved within these ganglia in a dormant state since the original episode of varicella. This results in pain and characteristic cutaneous findings (see History) along the corresponding sensory dermatomes of the involved ganglia. Less often, involvement of anterior and posterior horn cells, leptomeninges, and peripheral nerves is observed, with consequent muscle weakness or palsy, pleocytosis of spinal fluid, and/or sensory loss. Rarely, myelitis, meningitis, encephalitis, or visceral involvement may occur.

Frequency

United States

The incidence of zoster is estimated at 2-3 cases per 1000 per year (approximately 750,000 cases per year). Actual incidence may be significantly higher since many relatively mild cases do not come to the attention of health care workers and remain undiagnosed. Generally, approximately 10-20% of the US population eventually develops 1 or more cases of zoster. The incidence in individuals who are immunocompromised or in elderly persons is much higher, probably close to 50%.

International

Internationally, the incidence of zoster has not been well studied, but probably it is in the same range of 2-3 cases per 1000 persons per year.

Mortality/Morbidity

- Zoster is rarely, if ever, fatal, although in individuals who are severely debilitated, zoster may be considered a contributing factor to death.
- Morbidity usually is confined to pain within the affected dermatome, which can be severe and can persist well beyond the duration of active disease (postherpetic neuralgia [PHN]). Eye involvement (zoster ophthalmicus) can cause temporarily or permanently decreased visual acuity or blindness. Complications such as secondary infection and meningeal or visceral involvement can produce further morbidity in the form of infections and scarring.

Race

Blacks are reported to have a significantly lower risk of developing zoster than whites; however, zoster has been reported as an early manifestation of HIV infection in young Africans.

Sex

No sex predilection is reported for varicella-zoster virus reactivation.

Age

Almost 50% of individuals who live beyond age 80 years can expect to develop zoster. Zoster is rare in children and young adults, with the exception of younger patients with AIDS, lymphoma, other malignancies, and other immune deficiencies, and patients who are recipients of bone marrow and kidney transplants. In addition, patients with these associated factors are at greater risk of developing zoster regardless of age.

Clinical

History

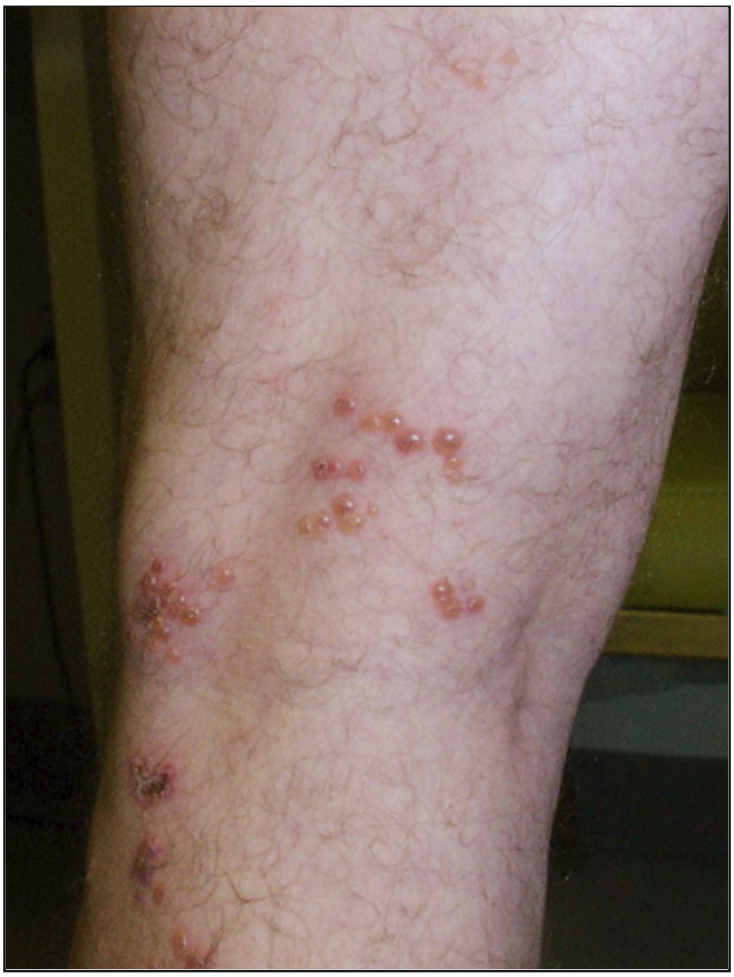
- Zoster may begin with a systemic response, eg, fever, anorexia, and lassitude, although symptoms frequently are mild and may not be associated by either patient or physician with the classic zoster signs and symptoms that follow.
- Symptoms typically include prodromal sensory phenomena along 1 or more skin dermatomes lasting 1-10 days (averaging 48 h), which usually are noted as pain or, rarely, paresthesias.
    - Prodromal pain typically is described as muscle or toothachelike in origin but may simulate headache, iritis, pleurisy, brachial neuritis, cardiac pain, appendicitis or other intraabdominal disease, or sciatica, which can result in incorrect tentative diagnoses.
    - The prodromal interval of pain prior to onset of cutaneous findings has been believed to represent spread of viral particles along sensory nerves; however, approximately 10% of patients report onset of pain and rash simultaneously.
- After the onset of prodromal symptoms, the following signs and symptoms occur:
    - Patchy erythema, occasionally accompanied by induration, appears in the dermatomal area of involvement.
    - Regional lymphadenopathy may appear at this stage or subsequently.
    - The classic finding of grouped herpetiform vesicles develops upon the erythematous base. At this point, the virus usually has induced significant inflammation of the involved sensory nerve causing severe pain, which led 19th-century French physicians to refer to zoster as "the band of roses from hell."

- Cutaneous findings classically appear unilaterally (for unknown reasons), stopping abruptly at the midline of the limit of sensory coverage of the involved dermatome. Vesicles initially are clear, but eventually, they cloud, rupture, crust, and involute. This evolution often is accelerated greatly by treatment.
- After vesicular involution, remaining erythematous plaques slowly resolve, typically without visible sequelae; however, scarring can occur if deeper epidermal and dermal layers have been compromised by excoriation, secondary infection, or other complications.

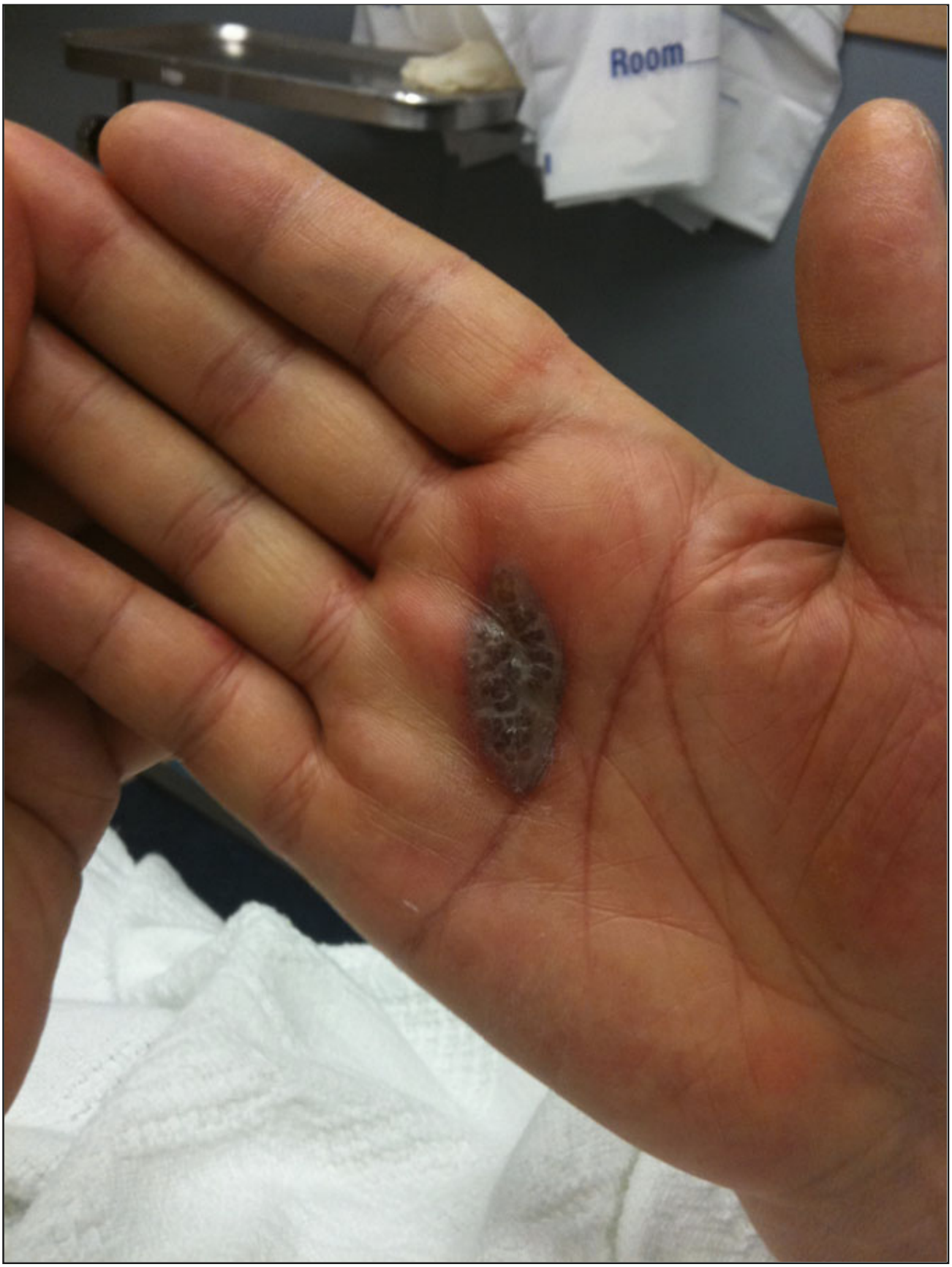
- Unfortunately, resolution of the associated pain does not always accompany resolution of erythema and vesiculation. PHN, which usually is confined to the area of original dermatomal involvement, can persist for weeks, months, or years and often is severe. The reason some patients with zoster, and not others, experience PHN is not understood fully, but patients who are older (>60 y), particularly patients who are debilitated or arteriosclerotic, are affected far more frequently than patients who are younger. In addition, PHN is observed more frequently after cases of herpes zoster ophthalmicus and in instances of upper body dermatomal involvement. Other less common postherpetic sequelae include hyperesthesia, or more rarely, hypesthesia or anesthesia in the area of involvement.
- The virus that causes zoster is morphologically and antigenically identical to the virus that causes varicella. In one study involving the recently released high-potency, live attenuated varicella-zoster virus vaccine developed by Merck, a reduction in the incidence rate of herpes zoster of 51.3% during 3 years of follow-up was noted.

Physical

Classic physical findings of zoster include painful grouped herpetiform vesicles on an erythematous base confined to the cutaneous surface innervated by a single unilateral sensory nerve. Regional lymphadenopathy may be present. Vesicles initially are clear but eventually cloud, rupture, crust, and involute. Note the images below.



Typical zoster in the vicinity of right popliteal fossa in a vertebral nerve L4 distribution.


Room

Suspected zoster of the hand.

Many clinical variations are possible as follows:

- Herpes zoster ophthalmicus (HZO) constitutes 10-15% of zoster cases.[1] HZO results from viral invasion of the Gasserian ganglion.
  - For unknown reasons, involvement of the ophthalmic branch of the fifth cranial nerve (CN; termed CN V1) is 5 times as common as involvement of the maxillary (CN V2) or mandibular (CN V3) branches. HZO is recognized easily by vesicular and erythematous involvement of the CN V1 dermatome, ipsilateral forehead, and upper eyelid.
  - Ipsilateral preauricular and, occasionally, submaxillary nodal involvement is a common prodromal event in HZO and often is valued equivalently with pain, vesiculation, and erythema in establishing a diagnosis.
  - Prodromal lymphadenopathy should not be confused with later reactive adenopathy caused by secondary infection of vesicles.
  - Headaches, nausea, and vomiting also are common prodrome symptoms.
  - Signs of meningeal irritation may be present; therefore, meningitis must be excluded.
  - The ophthalmic branch of the fifth CN (with ciliary ganglion) sends branches to the tentorium (recurrent nerve of Arnold) and to the third and sixth (and occasionally fourth) CNs, which may account for the frequency of meningeal signs and, occasionally, the CN III and CN VI nerve palsies associated with HZO.
  - HZO requires particularly aggressive treatment and follow-up monitoring because of the possibility of involvement of the eye, which occurs in approximately one half of patients with HZO.
  - Traditionally, involvement of the nasociliary branch, characterized by vesicles at the tip of the nose, has indicated that eye involvement is present or imminent (termed the Hutchinson rule). However, in recent years, clinicians with extensive experience in the treatment of HZO have disputed this, claiming that eye and nasociliary branch involvement can be present with or without distal nasal vesiculation. In the author's experience, eye lesions are rare in the absence of distal nose lesions.
  - Eye involvement poses a risk to vision in the absence of prompt detection and treatment. The presence of orbital edema is an ophthalmologic emergency, and patients must be referred immediately for specialized ophthalmic evaluation and treatment. Iritis, iridocyclitis, glaucoma, and corneal tissue ulcerations are possible in these cases. Involvement of the area below the palpebral fissure alone, without upper eyelid or nasal involvement, is considered less likely to result in ocular complications since the superior maxillary nerve innervates the lower eyelid.
  - Postherpetic complications are more common in HZO than in other manifestations of zoster. In particular, PHN is observed in well over one half of patients with HZO and can be severe and long lasting. Scarring also is more common, probably as a result of severe destructive inflammation. Palsy of the third CN, and occasionally of the fourth and sixth CNs, may occur. Rarely, simultaneous involvement of other CNs has been reported. The most common of these is seventh CN involvement, which may produce facial palsy.
- Zoster of the maxillary branch of the fifth CN (CN V2): Involvement is localized to the ipsilateral cheek, lower eyelid, side of the nose, upper eyelid, upper teeth, mucous membrane of the nose, nasopharynx, tonsils, and roof of the mouth. At times, only the oral mucus membrane is involved without skin manifestations. Early preeruptive herpetic pain can simulate a severe toothache and result in unnecessary oral surgery or dental treatment.

- Zoster of the mandibular branch of the fifth CN (CN V3): Areas of involvement include the side of the head, external ear and external auditory canal, lower lip, and a portion of the oral mucosa. As in other fifth CN branch involvement, prodromal pain in affected areas can result in incorrect diagnoses.
- Zoster oticus (also termed geniculate zoster, zoster auris, Ramsay-Hunt syndrome, Hunt syndrome): This form of zoster is considered rare but more likely is recognized rarely. It often is mistaken for eczema, Ménière disease, Bell palsy, stroke, and abscess of the ear. Classically, it begins with otalgia and herpetiform vesicles on the external ear canal with or without features of facial paralysis resulting from facial nerve (CN VII) involvement, auditory symptoms (eg, deafness), and vestibular symptoms in variable combinations. The syndrome also may result from zoster of ninth or tenth CN origin since the external ear has complex innervation by branches of several CNs (CN V, CN VII, CN IX, CN X), as well as vertebral nerve C2 and possibly C3.
- Glossopharyngeal and vagal zoster (herpes pharyngis, herpes laryngis): This variation of zoster involves the jugular and petrosal ganglia, which are adjacent and often involved in some combination; however, individual involvement of both ganglia has been observed. Painful vesicular rash typically involves the palate, posterior tongue, epiglottis, tonsillar pillars, and, occasionally, the external ear. A unilateral distribution can distinguish this variation of zoster from herpes simplex and herpangina.
- Herpes occipitocollaris (vertebral nerves C2 and C3 involvement): Involvement includes the posterior scalp, nuchal area, portions of the ear, and portions of the lower mandible and anterior neck. Vertebral nerves C2 and C3 often are involved together. Branches of vertebral nerves C2 and C3 communicate with the seventh and tenth CNs, sometimes causing CN VII and CN X symptoms as well. Nuchal and/or scalp involvement occasionally is confused with folliculitis, furunculosis, cellulitis, erysipelas, or acne keloidalis nuchae. The painful prodrome can result in confusion and misdiagnosis until the classic vesicular rash appears.
- Zoster encephalomyelitis (meningoencephalitis): Localized mild leptomeningitis in the region of neurologic involvement is more common than generally is recognized and often results in pleocytosis (25-50 lymphocytes) in the spinal fluid.
    - Leptomeningitis most likely occurs when CNs (especially fifth) are involved because of the presence of the recurrent nerve of Arnold, branching from CN V1 to the tentorium. For this reason, meningeal symptoms (headache, changes in sensorium, fever, stiffness of neck) are most common with HZO.
    - Rarely, symptoms of meningoencephalitis may be significant and, at times, severe enough to cause death. Reports exist of zoster encephalomyelitis being mistaken for acute poliomyelitis. Spread of varicella virus to the central nervous system also may occur during suppression of host resistance by neoplasms, by cytotoxic drugs, and, possibly, by radiation therapy.
- Zoster myelitis: That varicella-zoster virus can produce encephalomyelitis is well documented. More rarely, the myelitis lesion predominates or is the sole feature. The clinical picture is one of acute onset of paraplegia resulting from a diffuse involvement of the spinal cord. The picture is that associated with acute transverse myelopathy.
- Disseminated zoster: Dissemination usually is defined as a generalized eruption of more than 10-12 extradermatomal vesicles occurring 7-14 days after the onset of classic dermatomal zoster. Disseminated zoster typically is indistinguishable clinically from varicella (chickenpox).
    - Dissemination occurs in approximately 2% of zoster cases in the general population, but it has been observed in as many as 35% of patients who are hospitalized and/or immunocompromised.
    - Dissemination often is an indication of depressed cell-mediated immunity caused by various underlying clinical situations, which include malignancies, radiation therapy, cancer chemotherapy,

organ transplants, and the chronic use of systemic corticosteroids. However, the short-term use of low-to-moderate doses of corticosteroids has been shown not to increase the incidence of dissemination.

- Patients in whom zoster has disseminated must be observed carefully for the development of pneumonitis and encephalitis, which can be life threatening.

- Bilateral zoster: On rare occasions, zoster manifests bilaterally. The reason this occurs is unknown, as is the reason zoster typically occurs unilaterally. A popular superstition among lay people states that "if shingles occurs on both sides and meets in the middle, you will die." While some cases of bilateral zoster have been reported in patients who are extremely debilitated and in whom bilateral presentation cannot be considered a favorable sign, a fatal prognosis is not necessarily indicated for all patients. In cases of bilateral zoster, it is not unusual for 1 or 2 adjacent dermatomes to be involved. Unlike examples of multiple dermatomal involvement in unilateral disease, involvement in adjacent dermatomes is not typically a sign of underlying disease (eg, malignancy).
- Multiple dermatomal involvement: Involvement of more than 1 dermatomal distribution in unilateral zoster is rare and usually is considered a harbinger of significant compromise of the immune system caused by AIDS, malignancy, chemotherapy, and other factors.
- Recurrent zoster: Recurrences, while rare, are not unheard of and have not been shown to represent any specific event. Most reputed cases of recurrent zoster involve other entities, usually herpes simplex in a linear distribution.
- Zoster involving the urinary bladder: Rarely, zoster involving the dermatomes of the buttock area (vertebral nerves L1, L2, S2, S3, S4) may be associated with vesicles in the bladder, which can cause severe dysuria and urinary frequency. This picture can be mistaken easily for cystitis. If vesicles rupture in the bladder, hematuria (another common symptom of cystitis) may occur. Transient bladder paralysis resulting from zoster involving the gluteal and sacral regions and lumbar sympathetic segments has been reported, and acute urinary retention is possible if a motor component exists.
- Other internal manifestations: Vesicular involvement has been reported in bronchi, pleural spaces, and the gastrointestinal tract. Zoster pneumonia also has been reported. Such involvement frequently is found in individuals with significantly compromised immune systems. Pain in these areas, as on the cutaneous surface, may be referred pain and does not necessarily indicate the presence of vesicles.
- Motor complications: While zoster classically invades only sensory nerves (for unknown reasons), viral particles occasionally cross over to the anterior horn of the involved ganglion, resulting in motor symptoms.
    - Paresis may be seen in extraocular muscles, any area of facial innervation, and anywhere along the spinal cord, including the phrenic nerve. Paresis most commonly is observed when muscles of an arm or leg are involved; however, this may be because it is detected most easily at those locations.
    - Truncal motor involvement may be more common than generally is believed, because both physician and patient easily may overlook a small area of muscle weakness of the central trunk.
    - Motor symptoms can range from weakness to total paralysis, depending on how many roots of the involved nerve plexus are affected. While most motor involvement (like most sensory involvement) is self-limited, partial or complete paresis can persist indefinitely, particularly when CN V, CN VII, phrenic, and upper or lower extremity nerves are affected.
    - Paralysis of abdominal musculature can cause a hernial bulge.

Causes

- Reactivation of varicella virus that has remained dormant within dorsal root ganglia, often for decades after the patient's initial exposure to the virus in the form of varicella (chickenpox), causes zoster. Exactly what triggers this reactivation has not yet been determined precisely, but likely candidates include external reexposure to the virus, acute or chronic disease processes (particularly malignancies and infections), medications of various types, and emotional stress. More than 1 or all of these factors, plus others, possibly are capable of triggering zoster. The reason 1 dorsal root ganglion experiences reactivation of its stored viral load preferentially over other ganglia is unclear.
- Zoster can be a presenting symptom of hyperparathyroidism, and it occurs twice as often (rate, 3.7%) among patients with hypercalcemia compared with age-matched cohorts of patients older than 40 years who have normal calcium levels.[2]
- The cause of PHN also remains a mystery. Rapid initiation of treatment has been shown to decrease the incidence of PHN significantly, which can be explained by the theory that incessant pain of active zoster sets up a positive feedback loop within the thalamus and the cortex, creating a central pain syndrome similar to phantom leg pain. Prompt treatment breaks the loop by providing pain-free periods early in the disease course.

Differential Diagnoses

Acne Keloidalis Nuchae
Acneiform Eruptions
Aphthous Stomatitis
Candidiasis, Mucosal
Cellulitis
Chickenpox
Contact Dermatitis, Allergic
Contact Dermatitis, Irritant
Contact Stomatitis
Cowpox Infection, Human
Ecthyma
Erysipelas
Erysipeloid
Folliculitis
Herpes Simplex
Insect Bites
Jellyfish Stings
Lichen Striatus

Other Problems to Be Considered

Meningitis (see Workup)
Dental infection or abscess (zoster of CN V2)
Eczema
Ménière disease
Bell palsy
Stroke
Abscess
Herpangina
Furunculosis
Leptomeningitis
Meningoencephalitis
Myelitis
Cystitis

Workup

Laboratory Studies

- Systemic manifestations are uncommon and usually are confined to patients in whom the immune system has been compromised by other disease processes or chemotherapy. General laboratory studies and other systemic workup are not indicated unless complications or underlying diseases are suggested. A small percentage of patients, particularly those with CN involvement, may develop headache and neck stiffness, necessitating a spinal tap to exclude meningitis.
- Occasionally, Tzanck preparation, viral culture, direct fluorescence antibody (DFA) testing, and/or skin biopsy may be necessary to establish the diagnosis in atypical cases. DFA testing is more sensitive than conventional viral cultures because of the lability of varicella-zoster virus (VZV).
- Zoster is seen approximately 7 times more frequently in patients infected by human immunodeficiency virus (HIV); therefore, when clinically indicated, order an HIV test.
- Zoster occasionally is considered a harbinger of other occult disease, particularly malignancies in older patients. Studies in hospitalized populations show an increased incidence of zoster in patients with cancer, particularly those of the lymphoreticular system. However, prospective studies on nonhospitalized patients have not demonstrated any difference in incidence between patients with malignancies and those without. Both zoster and malignancy are common in elderly individuals; therefore, most experts currently consider the association to be purely coincidental.

Histologic Findings

Clinical diagnosis almost always can be made. Biopsy is reserved for cases difficult to diagnose. On rare occasions when biopsy is necessary, histologic findings are similar to those of herpes simplex and varicella (chickenpox). Ballooning degeneration and acantholysis of keratinocytes result in an intraepidermal vesicle. Multinucleated giant cells with accentuation of nuclear material at the periphery of nuclei are characteristic. Underlying leukocytoclastic vasculitis often is a prominent finding and helps differentiate zoster from other herpetic infections.

Treatment

Medical Care

An enormous number and variety of therapeutic approaches to the treatment of zoster have been proposed over the years, most of which probably are ineffective.[3] Reports of anecdotal evidence of efficacy are difficult to evaluate objectively because of the highly variable and self-limited nature of the disease.

Several guidelines related to treatment are available, with summaries as follows:

- International Association for the Study of Pain - Recommendations for the management of herpes zoster[4]
- Centers for Disease Control and Prevention -Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). 2) Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine[5]
- Centers for Disease Control and Prevention - Prevention of herpes zoster[6]
- American Academy of Pediatrics -Prevention of varicella: recommendations for use of varicella vaccines in children, including a recommendation for a routine 2-dose varicella immunization schedule[7]
- Systemic steroids: Many practitioners have long used oral prednisone and similar medications to reduce acute pain.[8] Some have also hoped to decrease the incidence of PHN, presumably by reducing inflammation in dorsal root ganglia and involved sensory nerves. While never conclusively demonstrated

in a double-blind crossover study, some evidence exists that steroids are effective in achieving this. More study is needed.

- A substantial dose (40-60 mg every morning) typically is administered as early as possible in the course of the disease and is continued for 1 week, followed by a rapid taper over 1-2 weeks.
- Dissemination of viral particles beyond dermatomal limits always has been a theoretical concern, but clinically, it almost never is observed in individuals with intact immune systems.
- Typical risks inherent in the use of systemic steroids, such as adrenocortical suppression and femoral osteonecrosis, must be kept in mind.

- Systemic antiviral agents
  - Controversy over use of systemic steroids has been rendered all but moot in recent years with the advent of effective antiviral agents.
  - Acyclovir and its derivatives (valacyclovir, famciclovir, penciclovir, and desciclovir, which is not available in the United States) all have been shown to be safe and effective in the treatment of active disease and in the prevention of PHN.
  - Usually, the earlier antiviral medications are started, the more effective they are in shortening the duration of zoster and in preventing or decreasing severity of PHN. Ideally, initiate therapy within 72 hours of the onset of symptoms.

- Varicella-zoster vaccine
  - Since 1995, live attenuated varicella virus vaccine (Varivax) has been available in the US and has been up to 99% effective in protecting susceptible individuals from varicella infection. The higher-potency vaccine introduced in 2005 (Zostavax) appears effective in preventing zoster.
  - It has been proposed that zoster occurs when varicella antibody titers and varicella-specific cellular immunity drop to a level at which they no longer are completely effective in preventing viral invasion. Evidence for this hypothesis includes observation that pediatricians, who presumably are reexposed to varicella virus routinely and thus maintain high levels of immunity, seldom develop zoster. Indeed, administration of varicella vaccine to older individuals whose antibody titers and cellular immunity have fallen over time appears to decrease their risk of developing zoster. The high-potency, live attenuated varicella-zoster virus (VZV) vaccine introduced by Merck (Zostavax) has demonstrated a reduction in the incidence rate of herpes zoster of 51.3% during 3 years of follow-up in one study.[9]
  - Prevention or attenuation of zoster is desirable in older patients because zoster is more frequent and is associated with more complications in older populations and because declining cell-mediated immunity in older age groups is associated with increased risk of zoster.
  - As of October 2006, the US Centers for Disease Control and Prevention (CDC) has recommended that the zoster vaccine be given to all people aged 60 years of age and older, including those who have had a previous episode of zoster.
  - Persons with a reported history of zoster can be vaccinated. Repeated zoster has been confirmed in immunocompetent persons soon after a previous episode. Although the precise risk for and severity of zoster as a function of time following an earlier episode are unknown, some studies suggest it may be comparable to the risk in persons without a history of zoster. Furthermore, no laboratory evaluations exist to test for the previous occurrence of zoster, and any reported diagnosis or history might be erroneous. Although the safety and efficacy of the zoster vaccine have not been assessed in persons with a history of zoster, different safety concerns are not expected in this group.
  - Patients older than 60 years who are about to begin biologic therapy (eg, for psoriasis, rheumatoid arthritis, or other indicated diseases) should have Zostavax (along with any other appropriate

vaccines) administered before starting their course of biologic therapy. Conversely, Zostavax is a live-virus vaccine, which means it should not be given to patients who have already been started on biologic therapies.

- The vaccine is similarly contraindicated in patients receiving long-term corticosteroid treatment and in as patients receiving chemotherapy or radiation therapy for hematopoietic malignancies and solid tumors.
- The duration of protection with the zoster vaccine is not yet known. Long-term follow-up studies are now being undertaken to address that question.

- Varicella-zoster immune globulin: The CDC currently recommends administration of varicella-zoster immune globulin (VZIG) to prevent or modify clinical illness in persons with exposure to varicella or zoster who are susceptible or immunocompromised. VZIG provides maximum benefit when administered as soon as possible after the presumed exposure, but VZIG may be effective if administered as late as 96 hours after exposure. Protection after VZIG administration lasts for an average of approximately 3 weeks, according to the CDC.

- Management of PHN
  - Pain associated with zoster usually is the most debilitating symptom of the disease. Once established, pain is notoriously difficult to alleviate with traditional analgesics, including narcotics. The only consistently successful method of treating PHN is to prevent it via prompt treatment of acute zoster and its associated pain. While acute zoster pain and PHN are believed to result from different pathophysiologic mechanisms, it is clinically and experimentally impossible to determine when the 2 cross over, and some workers use the term zoster-associated pain to describe both acute and chronic pain as a continuum.
  - Initiation of antiviral therapy as early as possible in the course of acute zoster, and definitely within 72 hours of onset, has been shown to be effective in alleviating acute pain and preventing PHN in most patients.
  - A randomized clinical trial of oral analgesics for acute pain in patients with herpes zoster was conducted (n = 87; age 50 y or older). Treatment was begun within 6 days of rash onset and with worst pain within 24 hours. Patients were initiated on a 7-day course of famciclovir with controlled-release oxycodone, gabapentin, or placebo for 28 days. Discontinuing participation, primarily associated with constipation, occurred most frequently in patients randomized to controlled-release oxycodone (27.6%) compared with placebo (6.9%). Mean worst pain was reduced the first week with controlled-release oxycodone compared with placebo (P = .01). Gabapentin did not provide significantly greater pain relief than placebo, although the first week provided a modest reduction of pain.[10]
  - A randomized, double-blind, placebo-controlled study of extended-release gabapentin demonstrated improvement in average daily pain score in patients with acute herpes zoster. In those taking gabapentin, a reduction of pain of 50% or greater from baseline was reported by 25.5-28.8%, compared with 11.8% of patients taking placebo.[11]
  - Once PHN has developed, various treatments are available.
    - Gabapentin and pregabalin are commonly used.[12]
    - Topical capsaicin can also be helpful; its active ingredient depletes neurotransmitters at involved nerve endings. However, the cream must be applied at least 5 times per day to be effective, and pain may increase upon application for the first few days of therapy as accumulated neurotransmitters are released. Once neurotransmitter reserves have been depleted, any resultant pain relief is temporary.
    - Tricyclic antidepressants have been used with variable success.[13]
    - Epidural injections of anesthetic and corticosteroids have been shown to be of benefit to

some patients.[14]

Consultations

Consultation with the appropriate specialist may be indicated when symptoms point toward meningitis (herpes zoster ophthalmicus), dental disease (zoster of maxillary branch), ear infections or deafness (Ramsay-Hunt syndrome), oropharyngeal infections (zoster pharyngis/laryngis), meningoencephalitis, and encephalomyelitis; when motor complications are present; or when the urinary bladder, lungs, or gastrointestinal tract are involved.

Activity

Patients may self-restrict activity because of limitations imposed by pain. Additional advice from physicians is rarely, if ever, necessary.

Medication

The advent of oral antiviral agents has made the treatment of zoster possible, when effectively, none existed before. Acyclovir and its derivatives (famciclovir, penciclovir, valacyclovir) have been shown to be safe and effective in the treatment of active disease and the prevention of PHN. Usually, the earlier these medications are started, the more effective they are in shortening the duration of zoster and in preventing or decreasing the severity of PHN. Ideally, initiate therapy within 72 hours of onset of symptoms.

Antivirals

Direct antiviral effect on varicella virus. Nucleoside analogs initially are phosphorylated by viral thymidine kinase to eventually form a nucleoside triphosphate. These molecules inhibit HSV polymerase with 30-50 times the potency of human alpha-DNA polymerase.

Acyclovir (Zovirax)

Prototype antiviral agent and synthetic purine nucleoside analog with in vitro and in vivo inhibitory activity against human herpes viruses including herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), VZV, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell cultures, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.
Intravenous acyclovir is indicated for treatment of zoster infections in patients who are immunocompromised.

Dosing

Adult

800 mg 5 times/d for 7-10 d may shorten time to complete lesion scabbing, healing, and cessation of pain, may reduce duration of new lesion formation, and may reduce prevalence of localized zoster-associated neurologic symptoms (eg, paresthesia, dysesthesia, hyperesthesia)

Pediatric

<2 years: Not established
>2 years and <40 kg: 20 mg/kg/dose PO qid (80 mg/kg/d) for 7-10 d
>40 kg: Administer as in adults

Interactions

Concomitant use of probenecid or zidovudine prolongs half-life and increases CNS toxicity of acyclovir; phenytoin concentrations may be decreased with coadministration

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure or when using nephrotoxic drugs; has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies of this drug at high concentrations; do not exceed recommended dose; exposure of herpes simplex and VZV isolates to acyclovir in vitro can result in emergence of less sensitive viruses; possibility of appearance of less sensitive viruses in humans must be borne in mind when treating patients; relationship between in vitro sensitivity of herpes simplex or VZV to acyclovir clinical response to therapy has yet to be established; because of possibility that less sensitive virus may be selected in patients receiving acyclovir, advise all patients to take particular care to avoid potential virus transmission if active lesions are present while they are on therapy; in patients who are severely immunocompromised, physicians should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses, which may not respond fully to continued acyclovir therapy; instruct patients to consult physician if they experience severe or troublesome adverse reactions, become pregnant or intend to become pregnant, intend to breastfeed while taking orally administered acyclovir, or have other questions

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Famciclovir (Famvir)

Prodrug that when biotransformed into active metabolite, penciclovir, may inhibit viral DNA synthesis/replication. Synthetic acyclic guanine derivative that has demonstrated activity against HSV-1, HSV-2, and VZV.
Initiate therapy promptly as soon as herpes zoster is diagnosed. No data are available on efficacy of treatment started 72 h after rash onset.

Dosing

Adult

Recurrent HSV: 125 mg PO bid for 5 d
Primary HSV-1: 250 mg PO bid for 5 d
Herpes zoster: 500 mg PO tid for 7-10 d

Pediatric

Not established

Interactions

Coadministration of probenecid or cimetidine may increase toxicity; coadministration increases bioavailability of digoxin

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Efficacy has not been established in ophthalmic zoster, disseminated zoster, or in patients who are immunocompromised; caution in renal failure or coadministration of nephrotoxic drugs; adjust dose if CrCl <60 mL/min

Valacyclovir (Valtrex)

L-valyl ester of acyclovir. Rapidly converted to acyclovir, which has demonstrated antiviral activity against HSV-1, HSV-2, VZV, and other viruses.
Initiate therapy at earliest sign or symptom of herpes zoster; therapy is most effective when started within 48 h of onset of zoster rash. No data are available on efficacy of treatment started 72 h after rash onset.

Dosing

Adult

Herpes zoster: 1 g PO tid for 7 d

Pediatric

Not established

Interactions

Probenecid, zidovudine, or cimetidine coadministration prolongs half-life and increases CNS toxicity of valacyclovir

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure and coadministration of nephrotoxic drugs; associated with onset of hemolytic uremic syndrome; acute renal failure and CNS symptoms have been reported in patients with underlying renal disease who have received inappropriately high doses; in geriatric patients; precipitation of acyclovir in renal tubules may occur when solubility (2.5 mg/mL) is exceeded in intratubular fluid; in acute renal failure and anuria, patient may benefit from hemodialysis until renal function is restored; efficacy has not been established for treatment of disseminated herpes zoster or in patients who are immunocompromised

Vaccines

Elicit active immunization to increase resistance to infection. Vaccines consist of attenuated microorganisms or cellular components, which act as antigens. Administration stimulates antibody production with specific protective properties.

Varicella zoster vaccine (Zostavax)

Lyophilized preparation of Oka/Merck strain of live, attenuated VZV. Shown to boost immunity against herpes zoster virus (shingles) in older patients. Reduces occurrence of shingles in individuals >60 y by about 50%. For individuals aged 60-69 y, it reduces occurrence by 64%. Also slightly reduces pain compared with no

vaccination in those who develop shingles. Indicated for prevention of herpes zoster.

Dosing

Adult

<60 years: Not established
≥ 60 years: Following reconstitution with entire vial of diluent supplied, use separate sterile needle and syringe to withdraw entire contents of reconstituted vial and administer SC; administer in upper arm

Pediatric

Not indicated

Interactions

None reported

Contraindications

Documented hypersensitivity to vaccine or components (eg, gelatin, neomycin); history of primary or acquired immunodeficiency states (eg, leukemia, lymphomas, malignant neoplasms affecting bone marrow or lymphatic system, AIDS); immunosuppressive therapy including high-dose corticosteroids; active, untreated tuberculosis

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Common adverse effects include erythema, pain, tenderness, itching, and inflammation at injection site; may also cause headache; may cause extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressive therapy (see Contraindications); defer vaccination if fever or acute illness present; do not inject intravascularly; administer within 30 min of reconstitution; not a substitute for varicella virus vaccine (Varivax) for children

Follow-up

Further Outpatient Care

- After initial treatment, further care consists solely of monitoring the patient and remaining alert for complications, such as secondary infection, eye involvement, meningeal or visceral involvement, and for sequelae such as PHN.

Deterrence/Prevention

- Since 1995, live attenuated varicella-virus vaccine (Varivax) has been available in the US and has been up to 99% effective in protecting susceptible individuals from varicella infection. The new higher-potency zoster vaccine has likewise proven effective in prevention of zoster.
- It has been proposed that zoster occurs when varicella antibody titers and varicella-specific cellular immunity drop to a level at which they no longer are completely effective in preventing viral invasion. Evidence for this hypothesis includes observation that pediatricians, who presumably are reexposed to varicella virus routinely and thus maintain high levels of immunity, seldom develop zoster. Indeed,

administration of varicella vaccine to older individuals whose antibody titers and cellular immunity have fallen over time appears to decrease their risk of developing zoster. The high-potency, live attenuated varicella-zoster virus (VZV) vaccine introduced by Merck has demonstrated a reduction in the incidence rate of herpes zoster of 51.3% during 3 years of follow-up in one study.

- Varicella-zoster immune globulin: The CDC currently recommends administration of VZIG to prevent or modify clinical illness in persons with exposure to varicella or zoster who are susceptible or immunocompromised. VZIG provides maximum benefit when administered as soon as possible after the presumed exposure, but VZIG may be effective if administered as late as 96 hours after exposure. Protection after VZIG administration lasts for an average of approximately 3 weeks, according to the CDC.

Complications

- Pain within the affected dermatome can be severe and can persist well beyond the duration of active disease (PHN). Eye involvement (zoster ophthalmicus) temporarily or permanently can cause decreased visual acuity or blindness. Complications such as secondary infection and meningeal or visceral involvement can produce further morbidity in the form of infections and scarring.
- Zoster is rarely, if ever, fatal, although in individuals who are severely debilitated, zoster may be considered a contributing factor to death.

Prognosis

- Prognosis is excellent, although the pain of PHN, when it occurs, can range in intensity from uncomfortable to debilitating.

Patient Education

- First, instruct patients to ignore the advice of well-meaning relatives, neighbors, and friends who will regale them with tales of pain, suffering, and even death. For example, many of the author's patients have been told that if shingles blisters travel around both sides of the body and meet in the middle, the patient will die.
- As done at the author's institution, inform patients that zoster almost always is confined to 1 side of the body and that if a rash crosses the midline, it probably is not shingles, which alone makes "blisters meeting in the middle" pretty much impossible. Patients are informed that while zoster often is painful (and that pain can persist if not treated properly or early enough), shingles rarely is dangerous or life threatening.
- Inform patients that zoster is caused by the same virus that causes chickenpox and that the pox rash resolves but the virus remains, lying dormant in the nerve roots of the spine. Years later, a stimulus (which can be illness, medications, injury, stress, or some undiscovered factor) triggers the virus into action. The virus springs forth from a spinal nerve root and inflames that nerve.
- Inform patients that the nerve in question normally supplies feeling to a band of skin immediately above it, which can be on 1 side of the face or body or on 1 arm or 1 leg. When the chickenpox virus inflames a nerve, the band of skin it supplies becomes inflamed, too. The result is pain, tenderness, and groups of painful blisters on a red base. The reason 19th-century French physicians dubbed zoster the band of roses from hell is easy to imagine.
- Inform patients that a person exposed to someone who has shingles can contract chickenpox if the

person exposed has never had chickenpox before.

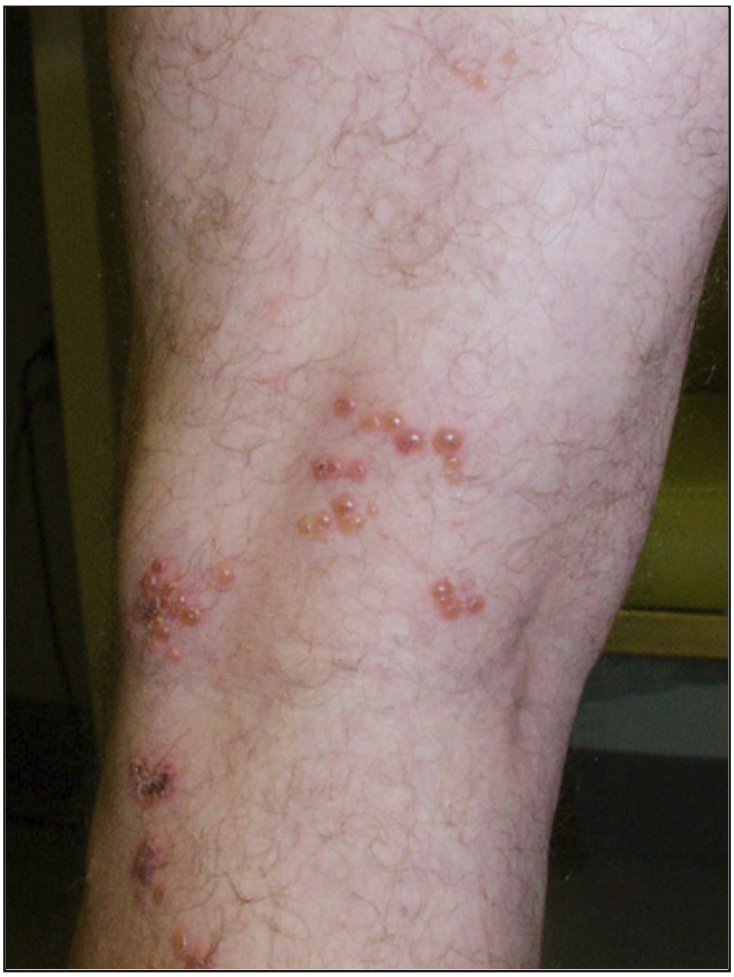
- Instruct patients that treatment should be started within 72 hours of onset if at all possible, not only to speed resolution of the shingles itself, but to prevent PHN. Once PHN begins, treatment is much more difficult and often unsuccessful.
- Finally, at the author's institution, special attention is given to HZO. Patients are informed that HZO often is more inflamed and more painful than shingles in other areas and occasionally results in pocklike scarring on the face if treatment is delayed. A close watch must be kept on the involved eye (sometimes in the hospital) to be sure the virus does not damage it. Severe cases require treatment by an eye specialist as well.
- For excellent patient education resources, visit eMedicine's Bacterial and Viral Infections Center. Also, see eMedicine's patient education articles Shingles and Chickenpox.

Miscellaneous

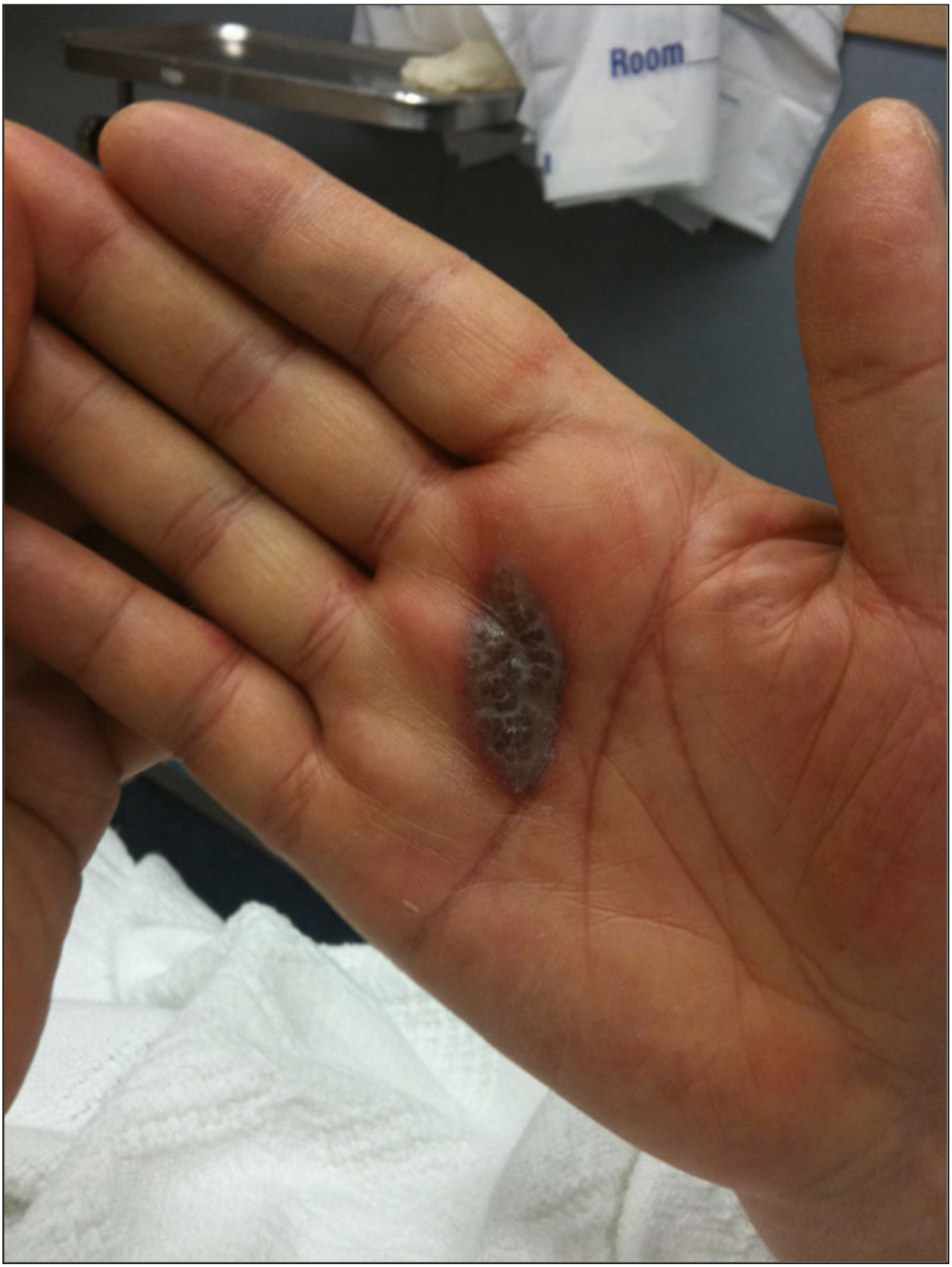
Medicolegal Pitfalls

- Failure to diagnose and treat zoster in a timely manner can result in increased acute pain, increased risk of complications such as secondary infection, and increased likelihood of PHN. The author has reviewed a lawsuit involving a patient who was immunocompromised in whom zoster was misdiagnosed and initiation of antiviral treatment delayed, allegedly resulting in severe chronic pain and significant decrease in functionality of the involved extremity.

Multimedia



Media file 1: Typical zoster in the vicinity of right popliteal fossa in a vertebral nerve L4 distribution.


Room

Media file 2: Suspected zoster of the hand.

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