Lineal erythematous painful plaque (LEPP) rule in herpes zoster infection: a simple clinical observation

Regla de la placa eritematosa dolorosa lineal (LEPP) en herpes zóster: una sencilla observación clínica

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ABSTRACT

Herpes zoster, or shingles, is a localized disease characterized by unilateral radicular pain and a rash limited to the area of skin innervated by a single dorsal root or cranial sensory ganglion. Whereas varicella, or chickenpox, results from primary exogenous varicella-zoster virus (VZV) infection, herpes zoster is caused by reactivation of latent endogenous VZV. Early diagnosis of herpes zoster is characterized by: *l*ineal, *e*rerythematous, *p*ainful, *p*laque (LEPP rule) in the first 24 to 72 hours, it has a favorable impact on instituting early treatment, reduces the severity of the disease and prevents the appearance of postherpetic neuralgia. Four immunocompetent patients with positive LEPP rule are presented.

KEYWORDS: *LEPP rule, varicella, herpes zoster, antivirals.*

RESUMEN

El herpes zóster es una enfermedad localizada que se caracteriza por dolor radicular unilateral y una erupción limitada al área de la piel inervada por una raíz dorsal única o un ganglio sensitivo craneal, mientras que la varicela es el resultado de una infección exógena primaria por el virus de la varicela zóster (VZV). El herpes zóster es causado por la reactivación del VZV endógeno que ha permanecido latente.[1,3,7]

El diagnóstico precoz del herpes zóster se caracteriza por una dermatosis lineal, eritematosa y dolorosa que forma una o varias placas (regla LEPP) presente en las primeras 24 a 72 horas, el inicio de un tratamiento temprano reduce la severidad de la enfermedad y previene la aparición de posneuralgia herpética. Se presentan los casos de cuatro pacientes inmunocompetentes con regla LEPP positiva.

PALABRAS CLAVE: *regla LEPP, varicela, herpes zóster, antivirales.*

Herpes zoster cases

Case 1

42-year-old male patient, at the time of the consultation presented several erythematous plaques on his back in a linear path, the surface is smooth and painful. The patient reports that he started with pain in the area for two days. Hematology and blood chemistry within normal limits. Treatment brivudine 125 mg daily for 1 week, obtaining excellent results (figure 1).

Case 2

A 34-year-old male patient, presented with painful erythematous plaques on the left aspect of the abdominal wall, grouped in a linear path. The patient reports that two days ago he suddenly presented pain in the region. Treatment acyclovir 800 mg every six hours, with excellent evolution (figure 2).

Case 3

A 60-year-old male patient with a 15 centimeters erythematous plaque on his back, extremely painful, and there are few papules on the surface. The patient reports that the previous night woke up a sudden pain in the region. Acyclovir 800 mg treatment every six hours. Satisfactory evolution (figure 3).

Case 4

A 67-year-old female presented in the proximal third of the right thigh and groin region a 15-centimeter painful

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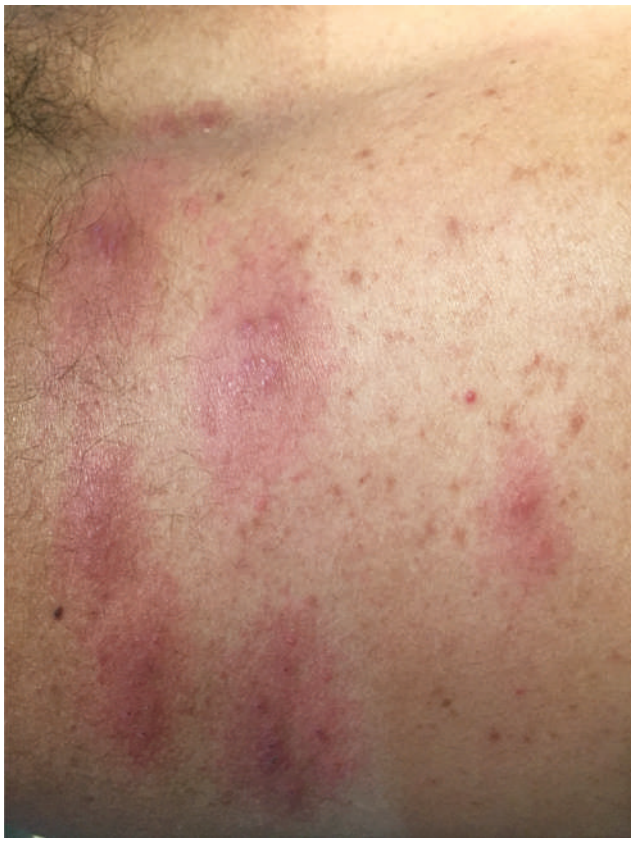

Figure 1. Erythematous plaques of back region.

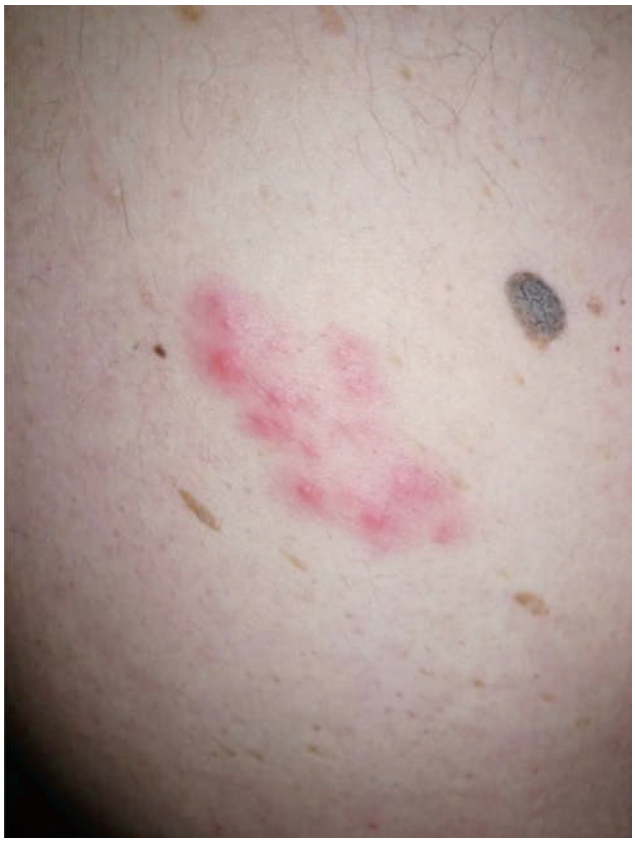

Figure 3. Erythematous plaque on back region.

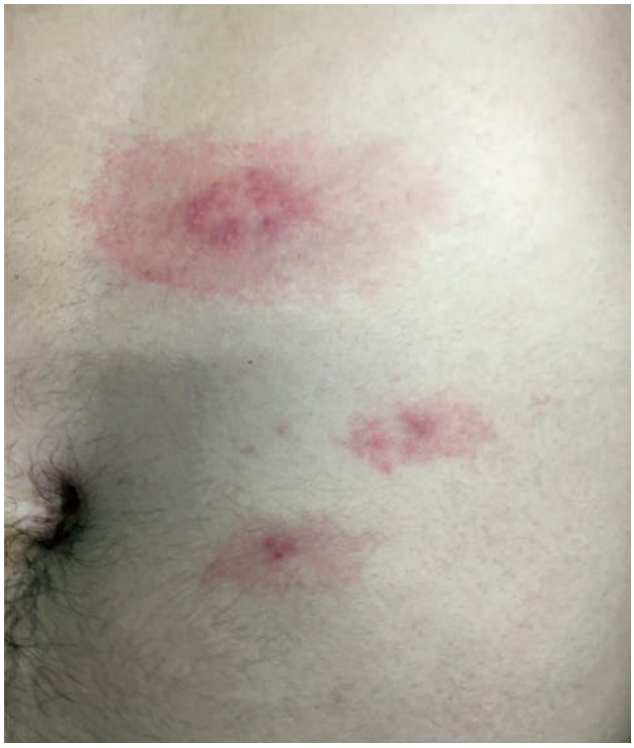

Figure 2. Erythematous painful plaques on the skin of the left aspect of the abdominal wall, grouped in a linear path.

smooth erythematous plaque. Patient refers that a sudden pain started two days ago making it difficult to walk. Lab tests within normal ranks. Treatment brivudine 125 mg every 24 hrs. Excellent response (figure 4).

Discussion

Only people who have previously had chickenpox are at risk of shingles. This infection and its complications increase with age, due to a decline in cell-mediated immunity to VZV.[3]

It mostly affects people aged over 60 years, but infants who contract chickenpox in their first year have an increased risk of developing it before 60 years-old, approximately 60% of people who develop shingles are female.[2,4]

Acute neuralgia is usually the first symptom and occurs in approximately 70 to 80% of patients. It is experienced as a localized tingling, itching, or burning sensation with intermittent stabbing pain. The type and intensity of pain can vary over time, but it usually persists through all three stages. Systemic symptoms can include malaise, fever, and headache can be present and has been reported in less than 20%. Lymphadenopathy can be present.[8]

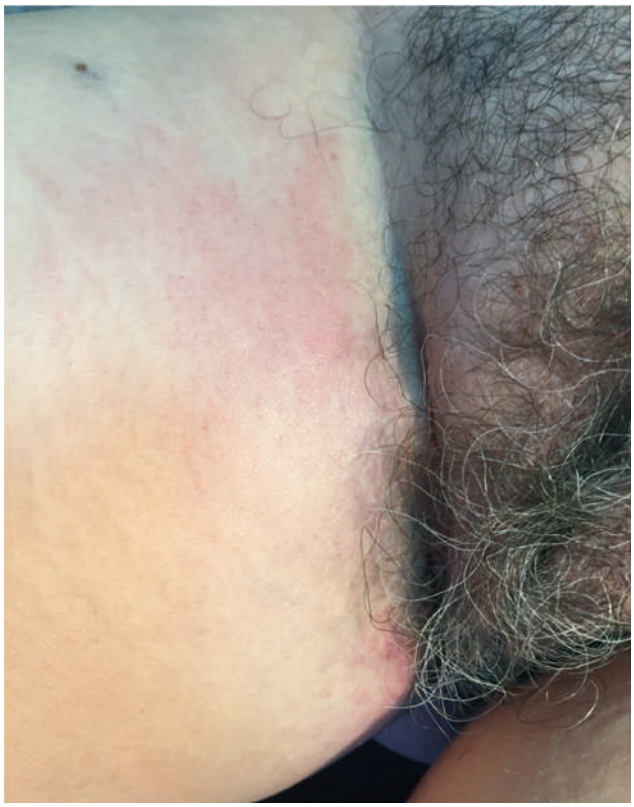

Figure 4. Erythematous painful plaque, on tight and groin region.

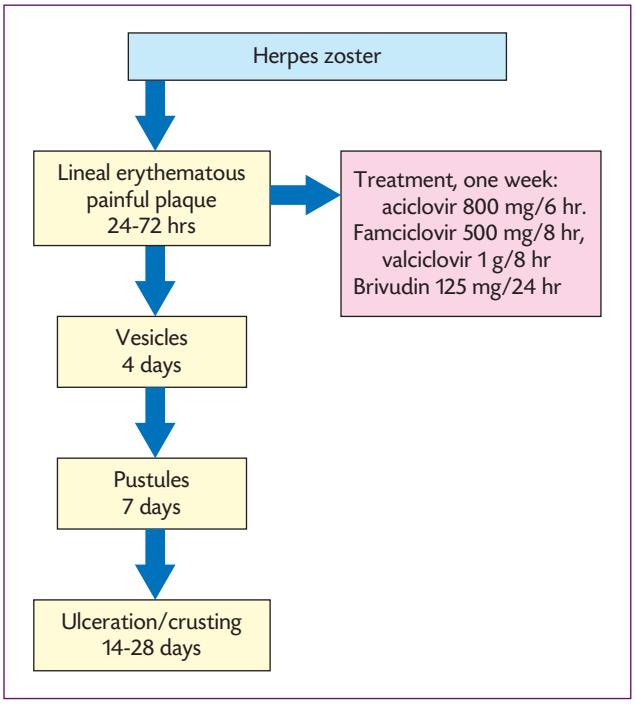

Figure 5. Evolution of skin lesions in herpes zoster.

It can be diagnosed based on the presence of the distinctive, painful dermatomal rash but it could be difficult to diagnose in the prodrome stage, prior to appearance of the rash. The differential diagnosis at this stage will vary widely and depend on the site and nature of the pain. Severe thoracic pain, for example, can be mistaken for cardiac or pleuritic chest pain.

The first stage is a brief erythematous and macular phase, which is often missed. Papules appear over the next three to four days and develop into vesicles within 1-7 days.[7] The vesicles then evolve to pustules within one week, followed by ulceration and crusting three to five days later[10] (figure 5).

Herpes sine herpete is a rare form that occurs without the rash; diagnosis is more challenging and is based on the presence of dermatomal pain and often laboratory investigation.[4] Once diagnosed, *herpes sine herpete* is managed in the same way. A patient with a rash but no pain is less likely to have shingles, although this can occur rarely, most often in young patients.[8] Other dermatological conditions that may be considered include herpes simplex, impetigo, atopic eczema or contact dermatitis.

Laboratory testing to investigate shingles is not routinely required. However, there are three tests available that may be requested to differentiate herpes simplex and zoster: sample from the base of a vesicle for the presence of VZV by immunofluorescence microscopy, real-time polymerase chain reaction (PCR) which can rapidly detect VZV DNA in skin lesion samples, and serological test can assess immunity to VZV.

Both immunofluorescence staining and real-time PCR are useful for distinguishing herpes simplex virus (HSV) from VZV.[9] Antibody testing can be used to confirm *herpes sine herpete* in patients without a rash but pain that is dermatomal distributed. The presence of VZV specific IgM antibodies in blood serum or cerebrospinal fluid indicates an acute infection.[11]

Antivirals are reported to reduce the duration of viral load, new lesion, and accelerate rash healing when given in the early stages. In a systematic review of antiviral treatment for post-herpetic neuralgia (PHN), four trials showed that patients treated with acyclovir within 72 hours of rash had a reduction in the incidence of acute pain four weeks after the rash.[12-14]

Meta-analysis of four double-blind, randomized, placebo-controlled trials of oral acyclovir (800 mg five times daily) was conducted to provide definitive assessments of the effect of acyclovir on the resolution of zoster-associated pain. The studies involved a total of 691 patients to evaluate pain sensation (Cox regression model) with adjustment for relevant prognostic factors (PHN) was also

determined at three and six months and half of the cases improved. Advancing age and more severe pain were associated with prolonged evolution. Acyclovir was clearly shown to accelerate pain resolution. Benefit was especially evident in patients 50 years-old and older.[15,16]

Famciclovir, the prodrug of penciclovir, is well absorbed from the gastrointestinal tract. It is then rapidly converted in the intestinal wall and liver to the active compound penciclovir, which has broad activity against varicella-zoster virus.[18] A placebo-controlled clinical trial was conducted in 419 immunocompetent adults (mean age 50 years) with uncomplicated zoster to evaluate the efficacy of standard-dose and high-dose (500 or 750 mg three times daily) with placebo. All patients initiated therapy within 72 hours of the rash and were treated for seven days. After five months of follow-up, famciclovir was associated with a modest improvement in lesion healing rates compared with placebo (median five to six *versus* seven days). While there was no difference in the incidence of PHN among the three arms, the use of famciclovir therapy, regardless of dose, conferred a selective reduction in the median duration of PHN compared with placebo (62 and 55 days with low-and high-dose famciclovir, respectively, *versus* 119 days.[16]

Valacyclovir is also well absorbed from the gastrointestinal tract. It is rapidly converted to acyclovir *in vivo,* thereby providing a three to fivefold increase in acyclovir bioavailability.

In a randomized, double-blind study of 1 141 immunocompetent adults with herpes zoster (mean age 68 years), the efficacy and safety of valacyclovir (1 000 mg orally 3/daily/7-14 days) was compared with acyclovir (800 mg orally 5/daily/7 days) over six months of follow-up. Cutaneous lesions resolved at similar rates in all treatment groups. However, valacyclovir for seven or 14 days accelerated the resolution of acute neuritis compared with acyclovir (median duration of pain 38 and 44 days, respectively, for valacyclovir compared with 51 days for acyclovir). In addition, the proportion of patients with pain persisting for six months was modestly lower in the combined valacyclovir arms, compared with the acyclovir arm (19 *versus* 26 percent). No additional benefit was observed with a longer duration of valacyclovir.[20]

Brivudine is a highly potent antiviral agent selectively active against VZV and HSV-1 with therapeutic equivalence to acyclovir. Because of concerns about potential toxicity, commercial development of brivudine has stopped in some countries (including the USA), but the drug is widely available in Europe and other countries. Brivudine (bromovinyl deoxyuridine; BDVU) is sequentially phophorylated by viral TK and cellular kinases to form BVDU triphosphate, a competitive inhibitor of viral DNA polymerase and alternate substrate for incorporation into viral DNA. The standard dose for herpes zoster is 125 mg orally daily for seven days. In randomized clinical trials, brivudine has been compared with acyclovir and famciclovir in immunocompetent patients with herpes zoster and was equivalent to other drugs for healing and pain resolution. With the daily dose, brivudine offers a potential advantage of convenience and improved patient adherence.[21]

The primary goal of this study was to compare efficiencies of famciclovir, valaciclovir, and brivudine in terms of pain relief in HZ patients. Records of patients who were admitted to the dermatology clinic due to acute HZ between the years 2012 and 2014 were retrospectively analyzed. Treatment decisions were at the discretion of caring physicians as valaciclovir (VACV), famciclovir (FCV), and brivudine (BRV) based on the clinical observations. BRV, FCV, and VACV were effective in treating pain in acute HZ. There was no significant difference between mild and moderate HZ patients. In severe cases, a significant reduction in intensity of pain was observed on day three in the BRV group, on day seven in the FCV group, and at two to three weeks in the VACV group. There were no significant side effects observed in any of the groups. Results of this study indicate that brivudine may be the first choice in severe HZ cases as it controls pain earlier and is easier to use because of its once daily administration.[22]

Conclusions

Early diagnosis of herpes zoster characterized by: *l*ineal, *e*rythematous, *p*ainful, *p*laque (LEPP rule) present in the first 24 to 72 hours, has a favorable impact on instituting early treatment, reduces the severity of the disease and prevents the appearance of PHN.

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