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Case Report

Herpes Zoster and Post Herpetic Neuralgia in an Older Adult who was later Diagnosed with Colon Cancer. Case Report and Review of the Literature

Rozenek Miriam*, Ramilo Maria del Carmen, Romani Adriana, Aronson Sandra, Camera Luis

Department of Internal Medicine, Hospital Italiano de Buenos Aires, Argentina

***Corresponding author**

Miriam Rozenek Pisterman, Department of Internal Medicine, Hospital Italiano de Buenos Aires, Argentina, Email: miriamrozenek@gmail.com

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Abstract

We feature the case of an 81 year old woman who presented thoracic herpes zoster (HZ) in November 2014, and although she was correctly and promptly treated with Aciclovir and different analgesic medications, presented a postherpetic neuralgia which was very difficult to treat as she couldn´t tolerate pain killers (digestive intolerance, falls and balance disturbances). After more than one year of the initial episode she was diagnosed with a colon cancer which she died for 15 months after the HZ episode.

We reviewed the literature and updated the topic of post herpetic neuralgia (PHN), its diagnosis, management, prognosis and prevention, and risk factors of HZ and PHN.

CASE REPORT

Eighty one year old woman, with the history of Chronic Stable Angina, non-affiliated arrhythmia treated with amiodarone, swallowing disorders (bronchoaspiration, use of thickeners), hypothyroidism and depression treated with mirtazapine 15 mg a day.

Innovember 2014, she consulted the Emergency Department for an acute chest pain and blisters which begun less than one day earlier. She was diagnosed Herpes Zoster and prescribed with oral Acyclovir 800 mg every 4 hours, 5 times daily, as well as topic Acyclovir, and acetaminophen plus tramadol for the pain.

One week later, and having finished oral Acyclovir, she asked for another consultation for the pain was not getting better. Pregabaline was added to the previous indications, given in increasing dosages in order to ease the pain. She also complained about pruritus. Paralellously her previous depression got worse as well as her insomnia, demanding a larger dose of mirtazapine. Three months after the beginning of the disease, she asked for consultation again with her GP. She was in great pain, as he had to abandon the painkillers because of digestive intolerance. Pregabaline was again initiated on a dosage of 25 mg three times daily, and also amitriptyline. Opioids were not re-indicated because of sickness. Pregabaline dosage was increased to 75 mg three times daily. Pain begun to slowly get better, and medications were well tolerated.

Six months after the initiation of HZ, she presented with falls, and had balance disturbances, which were attributed to pregabaline. Advise was given on fall prevention, but pregabaline remained the same, as pain was finally improving as well as her general status. Four months later, she was forced to abandon pregabaline and amitriptyline as falls and landing of balance advanced.

In November 2015 she begun to loose weigh, balance problems and neuralgic pain got worse, as well as tolerance to medication. She was seen by Pain Specialists who presecribeda local cream with 50% glucose , 5% lidocaine and 40% dimetilsulfoxide (DMSO).This somehow improved pain tolerance during the day, but worsened severely at night, interfering with sleep; so quetiapine was prescribed at night (12.5 mg). As pain and sleep disorders progressed, as well as her health condition worsened, she was put through new diagnostic tests. She was found to have anemia. Although she had had a videocolonoscopy performed 5 years earlier which had only showed colon diverticulosis, her physician asked for blood tests, abdominal sonogram, and other tests which were initially normal, except for the anemia. Some changes were done in her medications: mirtazapine was replaced by venlafaxine,pregabaline was given at bed time, and

intravenous iron was indicated. She did not improve, anemia increased, as well as pain, and weigh loss. By January she had already lost 8 kg in 5 months.

In February 2016 she presented with cachexia, and a urinary tract infection. Was admitted to hospital and other tests were performed. A double contrast CT Scan showedan asymmetrical circumferential thickening of the descending colon suggestive of primary neoformative process. A left hemicolectomy was performed, despite what she died less than a month later.

COMMENTS

Herpes zoster (HZ) is caused by reactivation of the Varicella Zoster virus (VZV). It affects peripheral nerves and causes painful skin and nerve lesions. The virus remains dormant in sensitive ganglia. Once reactivated, the virus moves along sensitive fibers up to the skin area they innervate. The virus causes direct inflammation and tissue damage, which is the underlying mechanism of neuralgic pain associated with HZ.

This reactivation triggers both, cellular and humoral immune response [1]. The cellular response is key in the protection of the disease, when it declines an appropriate scenario for the development of the episode is created. The episode itself works by stimulating cellular immunity, as if it were a natural booster that protects the patient from new episodes. The reactivation usually occurs most often in the elderly, or due to immune-suppression (HIV, cancer, corticosteroid chronically taken, etc). The recurrence of HZ is uncommon, only occurs between 1 and 5% of patients [2,3].

Both the incidence and severity of the episodes increase with age [4,5]. It is estimated that 20% -35% of people will develop HZ during their lifetime [6,7]. In most cases the diagnosis is clinical, although sometimes antigen detection techniques such as immunofluorescence, or detection of viral DNA by PCR [8].

Zoster usually presents as a blistered rash, unilateral, involving one to three dermatomes at the most [9], and acute neuritic pain. Pain is the most common symptom of HZ. Prodromal pain usually appears in the dermatome where the rash subsequently does. It may be constant or intermittent and can precede the rash by days to weeks [10,11].

Increasing age is the main risk factor for the development of herpes zoster.It is estimated that 20% -35% of people will develop HZ during their lifetime, with an incidence from 1.5 to 4.0 cases per 1000 people per year, peaking to 11 cases per 1000 people per year in their ninth decade of life [12,13]. Our working group found an incidence in elderly people in Argentina of 3.5 cases per 1000 people per year in the population between 60 and 64, to 6.6 cases per 1000 people per year in older than 85 years [14].

Other risk factors that enhance the reactivation of VZV are HIV infection, neoplastic disease, organ transplantation, use of immunosuppressive drugs, and other conditions that suppress the cell-mediated immunity[15].

Complications of HZ can include infections, central nervous system affection, nerve palsies, almost every single ophtalmic disorder, and post herpetic neuralgia (PHN), which, although is non life threatening, may be associated with an important loss of autonomy, poorer quality of life, and a significant cost for both the patient and the healthcare provider [7].

Neuralgic pain might develop before the rash, or during the acute phase of the disease. Typically 10% of those who experience acute pain, will still have it at one month following the rash onset. Post-herpetic neuralgia (PHN) is a direct consequence of the damage caused by VZV on the peripheral nerve and one of the most frequent complications in the elderly [16].

Post herpetic neuralgia

PHN is conventionally defined as the persistence of pain beyond 30, 60 or 90 days of eruption (17). It may last for months and even years.

PHN is the most frequent chronic complication of HZ and the most common neuropathic pain resulting from infection [18].

The incidence and prevalence of PHN vary depending on the definition used, but approximately a fifth of patients with HZ report some pain at 3 months after the onset of symptoms, and 15% report pain at 2 years [19,20].

PHN causes considerable suffering and results in a considerable health care burden. Patients with PHN have reduced quality of life, physical functioning and psychological well being [21].

The pharmacological management of this entity is of variable efficacy and little response in most cases. [22].

At a cellular level infection with acute HZ is characterized by hemorrhagic inflammation of the peripheral nerve, dorsal root, and dorsal root ganglion. Extension centrally into the spinal cord and leptomeninges also has been described. Fibrosis is noted in the dorsal root ganglion, nerve root, and peripheral nerve upon resolution of the acute process [23]. Autopsy data for cases of PHN are limited. One study reported five cases, three with severe PHN and two with no persistent pain. The findings included dorsal horn atrophy as well as cellular, axonal and myelin loss in the nerve and sensory toot were found in cases with and without pain [24].

Assessment of the patient with PHN

Features of pain and associated sensory perturbations (itching, paresthesias, allodynia, burning, etc) should be assessed. Pain associated with PHN may occur continuously, paroxystically (as electric shock like pains), and evoked sensations that are pathological amplifications of responses to light touch and other innocuous stimuli.

There are several questionnaires available that “measure“the quantity of pain, and its interference in daily life activities, such as the Zoster Brief Pain Inventory [25].

Physical examination should include a comparison of sensory function in the affected dermatome with that on the contralateral side. Loss of sensory function in response for both mechanical and thermal stimuli, as well as sensory amplifications to normal stimuli, are frequently found in patients with PHN. Generally no further examination is required.

Management of PHN

As seen in the patient discussed above, pain management is tough. It may require several drugs, for a great amount of time. The objective of the treatment of PHN is primarily pain alleviation and improvement of the quality of life [26].

It is important to monitor the effect of interventions on pain intensity, and on adverse effects rose by the use of drugs.

Antiviral therapy in the early acute phase significantly reduces the severity of infection, however, this therapy does not completely alleviate acute herpetic neuralgia. It also prevents the possibility of persisting pain such as PHN.

Randomized trials support the effectiveness of both topical and oral agents, however, PHN is very difficult and sometimes even impossible to treat despite the use of strong analgesics. Pathologic evidence suggests that VZV can cause permanent peripheral and central nervous system damage, destroying sites of intrinsic pain inhibitory mechanisms where analgesics act. That´s why patients respond poorly or are even almost refractory to all drugs for pain [27], as happened to our patient.

Treatment is based on symptom control. As pain may persist for years, and even sometimes for life, medication is often required for long periods of time. As the drugs used are not free of adverse effects, as seen in our patient, these should be monitored as well as the evolution of pain, in order to modify treatments, however this may be very difficult to achieve.

To point out the options available for PHN treatment, refer to table 1, and table 2 for the recommended treatment of neuralgic pain.

Topical treatment may be used alone in mild pain, or in combination with oral drugs.

As many of the patients with PHN are elderly, and usually take other prescriptions, a close monitoring of side effects and drug – drug interactions should be performed.

Prevention of PHN

Antiviral drugs for acute HZ have shown to reduce severity of acute pain and rash, hurry rash resolution and reduce the duration of pain. In Argentina we use Acyclovir and Valacyclovir. There is evidence that the early use of either of these medications, may help to reduce the risk of PHN [28-37]**.** In the case discussed above, our patient took the correct treatment which begun the day after the initiation of symptoms.

On the other hand, several trials demonstrated that the addition of steroids to antivirals at the initiation of treatment, did not reduce the incidence of PHN [38].

However, the only well documented means of preventing PHN is the prevention of HZ with the live attenuated VZV vaccine. This vaccine reduces the incidence of HZ by 51% and the incidence of PHN by 66% [39-42]. Comparing 60 to 69 year old patients with 70 years old or older as receiving the vaccine, it seemed to be less effective in reducing the risk of HZ (63.9% versus 37.6% reduction), but conferred similar protection against PHN 65.7 in 60 to 69 versus 66.8% in 70 and older.

HZ vaccine became available in our country in 2014, and is recommended for inmuno competent adults aged 60 to 70. It has still low acceptance, maybe because of its cost, and because it has no health insurance covering.

SUMMARY

As shown above, PHN may be a long, and very much affecting quality of life disease. Its treatment can present a challenge being that older adults are usually medicated with several drugs. So, drug / drug interaction and dosage should be evaluated at all times when prescribing.

In Argentina we followed 390 older adults after the acute HZ episode. (14) We found that 40.6% were still in pain after the end of the episode. 27% patients had PHN with an average duration of 138.7 days (range 60 days to 24 months). 93.8% of the patients had no immune status affecting conditions. The remaining 6.2%

Table 1: Available options for PHN treatment.

Topical treatment
• Lidocain5% gel (28) • Capsaicin cream (has to be applied several times a day, and besides that, causes a burning sensation and local eritema). Makesitdifficult to tolerate. • Capsaicin 8% patch (applied once daily, for 60 minutes) • Local cream 50% glucose, 5% lidocaine and 30 - 50% dimetilsulfoxide (DMSO).
Sistemic treatment
• Non steroidal anti-inflamatory drugs and acetaminophen (29) • Tryciclic antidepressants (avoid if heart disease, epilepsy or glaucoma) (30) • Gabapentin or pregabalin(common side effects: dizziness, somnolence, dry mouth, peripheral edema, weight gain, and risk of euphoria) (31) • Opioids (potential concern for abuse and addiction)(32, 33) • Valproic acid (Eight week randomized controlled trial of 48 patients. 58% patients had at least moderate improvement in pain relief)
Other treatments
• Intrathecal glucocorticoid injections (not suitable for pain distributed on the trigeminal nerve territory)(34) • Botulinum toxin injections (just one study with 30 patients showed benefits at 2 weeks, with benefits persisting at least 16 weeks)(35) • Cryotherapy (Freezing of peripheral nerves. Few patients. producing less than two weeks relief) (36) Surgery: including electrical stimulation of the thalamus, anterolateral cordotomy electrocoagulation of the dorsal root. (Substantial risks and no consistent benefits demonstrated) • Acupuncture (No clinicaltrials) • Transcutaneous electrical nerve stimulation (TENS), Transcranial magnetic stimulation (TMS) (not been proven)

Table 2: Recommendations for first line medication and Opioid Agonists for Neuropatic pain (27).

Medication class	Starting dosage	Tritation	Maximum dosage	Duration of adequate trial
Secondary(2°) amine TCANortriptiline or desipramina (Terciary amine TCA only if 2° not available)	25 mg bedtime	25mg/d every 3-7 d as tolerated*	150 mg/d	6 – 8 weeks with at least 2 weeks at maximum tolerated dosaje
SSNRIs Duloxetine Venlafaxina	30mg /daily 37.5mg once or twice daily	Increase to 60mg/d after 1 week Increase by 75 each week	60 mg twice daily 225 mg/d	4 weeks 4 – 6 weeks
Calcium Channel α^2 ligands Gabaentin[(A)] Pregabalin[(A)]	 100 -300 mg bedtime or 3 times daily 50mg 3 times daily or 75 twice daily as tolerated	 Increase 100-300 mg/d every 1 - 7 days as tolerated Increase to 300mg every 1-7 days as tolerated	 3600mg/d (1200 x 3). Reduce if impared renal function 600 mg/d (200 x 3 or 300 x 2). Reduce if impared renal function	 3-8weeks for tritation + 2 weeks maximum dosage 4 weeks
Topical lidocaine 5% lidocaine patch	Maximum 3 patches daily for a maximum of 12 hs	None needed	Maximum 3 patches daily for a maximum of 12- 18 hs	3 weeks
Opiois Agonists Morphine, oxycodone, methadone, levorphanol Tramadol[(A*)]	10-15 mg morphine every 4 hs or as needed 50 mg once or twice daily	After 1 -2 weeks convert total daily dosage to long acting opioid analgesic and continue short acting medication as needed Increase 50-100 mg/ d in divided doses every 3 -7 days as tolerated	No maximum dosage with careful tritation. Consider evaluation by pain specialist as relatively high dosages 400mg/d (100 x 4); in patients >75years: 300mg / daily	4 – 6 weeks 4 weeks

SSNRI selective serotonine norepinephrine reuptake inhibitor
TCA: tricyclic antidepressants
[A]: lower starting dosages and slower increasing dosage in older adults
[A*]: Consider lower starting dosages and slower increasing in older adults. Dosages given are for short acting formulations

had diabetes II: eight; Active cancer disease: eight; four were on immunosuppressive treatment for rheumatologic disease or transplantation, and one was HIV positive. The patient presented above was finally diagnosed with cancer, however we don´t believe there is an association between neither the episode of HZ nor PHN, with the patient´s colon cancer.

This case was difficult to manage because of medication intolerance and overlapping symptoms between PHN and cachexia. Both show hyporexia, sleep disorders, depression, and worsen of health status. In our patient the onset of symptoms associated with her colon cancer, concurred with those belonging to PHN, making it difficult to distinguish between them even now, knowing the final diagnosis.

PHN prevention is mainly achieved through the vaccine, which is recommended to individuals aged 60 to 70, independently of history of VZV infection, since more than 95% adults over 40 are immune to VZV, thus at risk for HZ [30].

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