



## Herpes Zoster: A Clinicopathologic Correlation with Literature Review

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### ABSTRACT

Herpes zoster is an acute infectious viral disease of an extremely painful and incapacitating nature. It is characterized by inflammation of dorsal root ganglia or extra medullary cranial nerve ganglia, associated with vesicular eruptions in the areas supplied by the affected nerve. Herewith we report a case of herpes zoster involving two branches—the maxillary and ophthalmic branch of trigeminal nerve. The demonstration of typical viral inclusion bodies by exfoliative cytology from the lesional site aided the rapid diagnosis of the lesion thereby facilitating an early initiation of therapy and improving patient compliance. The article also outlines the history, epidemiology and the natural course of the disease with a discussion of the review of literature.

**Keywords:** Zoster, Shingles, Viral infection, Herpes zoster, Post-herpetic neuralgia.

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### INTRODUCTION

Varicella zoster virus (VZV) is a DNA virus belonging to the family of herpes viridae family. It is known by many names including: chicken pox virus, varicella virus, zoster virus and human herpes virus type III (HHV-III).<sup>1</sup> The family name of all the herpes viridae is derived from the Greek word herpein meaning 'to creep'. Zoster is derived from the Greek word zōstēr, meaning 'belt' or 'girdle' representing the characteristic belt-like dermatomal rash. The common name for the disease, shingles is derived from the Latin word cingulus, a variant of the word cingulum meaning 'girdle'. Herpes zoster has a long winding history dating from as early as the 18th century. The historical accounts failed to distinguish the blistering caused by VZV and those of small pox, erysipelas, etc. It was in the late eighteenth

century that the differences between herpes zoster and smallpox was suggested by William Heberden, who later also came up with the differences between herpes zoster and erysipelas. Richard Bright suggested that herpes zoster arose from the dorsal root ganglion in the year 1831 which was later confirmed by Felix von Bärnsprung in 1861. The relationship of chicken pox and shingles was later proven by the Nobel laureate Thomas Huckle Weller, in 1953 for isolating the virus in cell culture.<sup>2</sup>

VZV causes two distinct lesions known as chicken pox and herpes zoster. Chicken pox is an acute, ubiquitous, extremely contagious disease usually occurring in children and is characterized by an exanthematous vesicular rash. It is an air-borne infection with the respiratory tract being the portal of entry. The virus lies dormant in the dorsal root spinal ganglion or the extramedullary cranial nerve ganglia of the infected person. Herpes zoster is caused by the reactivation of the dormant virus and involves the dermatome supplied by the sensory nerve that arises from the ganglion.<sup>3</sup>

Herpes zoster is sporadic in occurrence in contrast to chicken pox which is most common during the winter and spring months. It is predominantly a disease of the middle aged and elderly individuals. Less than 5% cases occur in children. The triggering factors include: immunosuppressive therapy, surgical stress, radiation therapy, physical trauma or an underlying debilitating disease such as diabetes mellitus, human immunodeficiency viral (HIV) infection, leukemia, Hodgkin's disease, or other malignancy.<sup>4</sup> Characteristically, the condition presents as a painful unilateral vesicular rash usually restricted to the distribution of the sensory nerve. The thoracolumbar trunk, especially T3 to L4 is more commonly affected. Cranial nerves are also occasionally involved, trigeminal nerve being the most frequently affected. It is usually unilateral and limited to a single division, more often the ophthalmic (first) branch. The complications of shingles include postherpetic neuralgia, being the most significant, to motor nerve palsy, encephalitis, optic neuropathy and blindness. In the present report, herpes zoster involving two branches (I and II) of the trigeminal nerve is discussed along with literature review.<sup>5</sup> This article also discusses the effective application of a simple and efficient investigative technique-exfoliative cytology, which reduces the time taken for diagnosis, thereby improving patient care.

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## CASE REPORT

A 45-year-old female reported to the Department of Oral Pathology, Faculty of Dental Sciences, Sri Ramachandra University, with the complaint of painful fluid-filled blisters on the right side of the face for the past 4 days. The patient was apparently normal a week ago when she suddenly developed fever and malaise. She experienced severe pain in the posterior region of the upper arch. This was followed by the appearance of blisters on the forehead which then spread to the mid-facial region. The severity of pain also increased with puffiness around the right orbital region.

The patient gave history of an episode of chicken pox at the age of 10 years. She did not suffer from any other systemic illnesses, no allergies; she was a nonsmoker and nonalcoholic.

On extraoral examination, a large diffuse swelling in the right half of the face was observed (Fig. 1). The facial skin appeared erythematous with some areas of hyperpigmentation. Numerous vesicles were distributed along the zygomatic prominence, upper lip region, forehead, nose and around the eye (Fig. 2). The vesicles were restricted to the right half of the face. Jaw movements and mouth opening were restricted. Intraoral examination revealed presence of vesicles in the right posterior aspect of hard palate.

The patient was quite irritable and non-co-operative as she could not tolerate the pain and wanted some form of rapid relief. A cytological smear was taken from the base of the lesion on the facial aspect which revealed Tzanck cells and multinucleated giant cells consistent with viral inclusions (Figs 3 and 4). Relating the previous episode of chicken pox with the existing clinical features we arrived at a clinic-pathologic correlation of Herpes zoster infection involving the ophthalmic and maxillary divisions of the Trigeminal nerve. The patient was advised acyclovir 800 mg

thrice daily for 1 week, analgesics, mouth rinses, and topical silverex ointment. The lesions healed well and follow-up revealed no complications.

## DISCUSSION

Herpes zoster, a cutaneous vesicular eruption resulting from the recrudescence of varicella zoster virus infection in humans is strongly associated with the middle aged to the elderly. After the initial infection of chicken pox, the provirus segments travel along the sensory nerve fibers and reside in the cranial/ dorsal root ganglia.<sup>6</sup>

Latency of varicella zoster virus is a widely researched topic. Many authors have contributed extensively to the molecular basis of latency and reactivation.<sup>7</sup> Gildeen et al,<sup>8</sup> Hyman et al,<sup>9</sup> using the technique of *in situ* hybridization suggest that it remains latent in the neurons while a few others suggest that it resides in the satellite cells which surround the neurons. Lungu et al suggest that the varicella zoster virus (VZV) nucleic acid is found in both the neurons and satellite cells. To further elucidate the fact of latency certain VZV proteins such as ORFS63 have been localized in the cytoplasm of neurons during the lytic phase. These proteins translocated to both the cytoplasm and nucleus of neurons in ganglia undergoing reactivation.<sup>10</sup>

The pathophysiology of reactivation still remains elusive. It is hypothesized that the reduction of VZV specific memory T cells with increasing age could trigger VZV reactivation. This also explains the predominance of the disease among the elderly. Deficient immunity poses a greater risk of the infection. Hence patients undergoing bone marrow/organ transplantation, diabetics and HIV positive individuals are at an increased risk for Herpes zoster.<sup>11</sup>

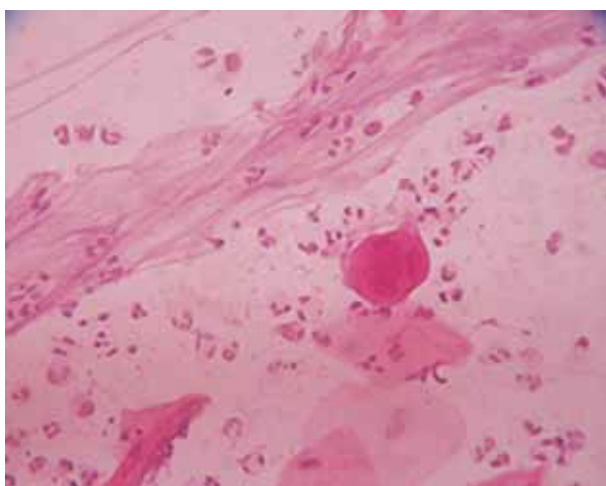
Trauma and other stressful conditions can cause VZV reactivation. Lin KC et al<sup>12</sup> reported a case of reactivation of herpes zoster in a middle aged man along the maxillary



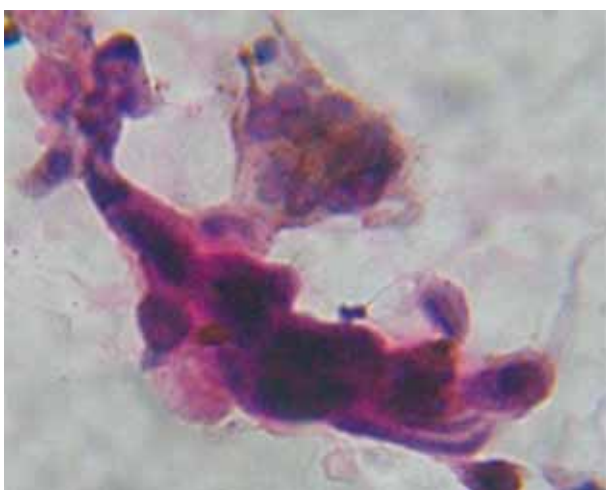
Fig. 1: Patient photograph depicting a diffuse swelling of the right side of the face



Fig. 2: Herpes zoster showing the typical unilateral dermatomal distribution of the vesicles



**Fig. 3:** Cytology depicting a virally altered epithelial cell surrounded by neutrophils consistent with secondary infection



**Fig. 4:** Cytological smear showing acantholytic cells and a characteristic multinucleated giant cell showing nuclear molding without overlapping and variation in nuclear size and shape

division of the trigeminal nerve following a facial trauma. The mechanism of reactivation of VZV following trauma could be attributed to reflex irritation and hyperemia of ganglion according to Weiss R.<sup>13</sup> Thoms et al reported a 12-fold increased risk of herpes zoster infection following a recent trauma.<sup>14</sup>

Herpes zoster is characterized by a prodromal phase that begins 2 weeks prior to the eruption of vesicles. The patients experience pain and paresthesia along the dermatome to be affected. Malaise, dysesthesia and itching/tingling sensation can also be perceived by some patients. The zoster rash appears proximally, and then spreads distally along the affected dermatome, usually the thoracic trunk. Among the cranial nerves, the ophthalmic branch of the trigeminal nerve is most commonly affected producing the characteristic herpes zoster ophthalmicus (HZO).<sup>11</sup> In the present case the ophthalmic and maxillary divisions (first and second

branches) of the trigeminal nerve was affected. No evidence of HZO was noted.

Terasaki S et al<sup>15</sup> reported an unusual case of herpes zoster of the second and third branches of the trigeminal nerve with a co-existing herpes labialis infection. Isolation of the viruses from the exudates was required to prove this simultaneous VZV and HSV infection.

Kasahara M et al<sup>16</sup> reported a rare case of Zoster sine herpette of the trigeminal nerve in which the typical vesicular eruptions of zoster are absent which can lead to a delay in the diagnosis of the disease. In such cases polymerase chain reaction (PCR) assays can clinch the diagnosis at a much earlier stage thereby improving the patient compliance. The authors conclude that zoster sine herpette should be considered in patients with severe facial pain over specific dermatomes if there are no appreciable findings of traumatic neuropathy, tumor or herpes zoster.

A number of potential complications of the disease such as encephalitis, myelitis and nerve palsies have been reported among the patients. Less than 5% of the patients present with Ramsay Hunt syndrome with features of hearing loss, vertigo and facial paralysis.<sup>1,5</sup> Granulomatous reactions such as granuloma annulare, pseudolymphoma, sarcoidal reaction and eruptive keratoacanthoma have been reported to occur at the site of the healing zoster scars. More than 60% of patients above 60 years of age develop postherpetic neuralgia, a chronic debilitating condition affecting the quality of life of the affected patients. Postherpetic neuralgia presents with chronic fatigue, anorexia, weight loss, insomnia and persistent/intermittent pain.

Bennett GJ has put forth two theories regarding post-herpetic neuralgia. One is due to the sensitization of the nociceptors during acute zoster phase and failure to return to their pre-zoster state. The second theory states that a persistent subclinical threshold of central hyper-sensitization causes the development of neurons that are more easily stimulated thereby causing the neuralgia.<sup>7</sup>

Manoj Kumar Jain et al<sup>5</sup> reported an unusual oral complication of osteonecrosis with spontaneous exfoliation of teeth and pathologic fracture of the mandible in a 65-year-old man with herpes zoster infection of the mandibular branch of the trigeminal nerve. Several hypotheses regarding the pathophysiology of alveolar bone necrosis were discussed. Those include-the neural inflammation causing a direct local vasculitis, a general infection of the nerves supplying the periosteum and periodontium of the dermatome involved, denervation of bone, a systemic viral infection of the odontoblasts leading to the necrosis of the tissues involved or a pre-existing pulpal/periodontal inflammation contributing to the alveolar bone necrosis.<sup>17</sup>

Diagnosis of Herpes zoster can frequently be recognized by the characteristic distribution of the lesions.<sup>1</sup> Cytology has a documented role in diagnosis of diseases. It is a quick, simple and efficient procedure which has a high value in the screening of lesions and reduces the time required for the generation of a report. Proper smear preparation and evaluation requires sufficient experience. Herpes zoster can be easily recognized by the presence of the multinucleated giant cells (Tzanck cells) and intranuclear inclusions. These multinucleated cells differ from the multinucleated foreign body giant cells in their characteristic nuclear molding without overlapping and variation in nuclear size and shape. Discrete intranuclear viral inclusions surrounded by halos can be observed. Many nuclei show a characteristic 'ground-glass' chromatin pattern. The cytoplasm of the infected cells has a hyaline appearance which may be followed by ballooning degeneration.<sup>18</sup> Advanced diagnostic techniques such as fluorescent antibody staining techniques, nested and real-time polymerase chain reaction tests can also be used for further analysis.<sup>1</sup>

Effective antiviral therapy should be promptly instituted to reduce the severity of the disease. The US FDA has recommended the usage of the Herpes zoster vaccine for persons aged 60 years and above. This helps in reducing the occurrence of the disease by half and the risk of post-herpetic neuralgia by two-thirds.<sup>19</sup>

## CONCLUSION

Herpes zoster is associated with significant morbidity especially in the elderly and immune-compromised patients. A thorough clinical examination coupled with a rapid and effective cytopathological examination helps in arriving at an early diagnosis. A prompt and effective treatment helps in reducing the post-herpetic complications thereby improving the quality of life of the affected patients.

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