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Case report

Clinical and Cytopathological Traits of Herpes Zoster: A Report of Two Cases

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SUMMARY

Introduction: Varicella zoster virus is a highly infectious α-herpesvirus, pathogenic only to humans. The primary infection of varicella zoster virus causes chickenpox, which is contagious and primarily infects children and adolescents in India. Following the primary infection, the virus remains dormant in sensory root ganglia. Activation of the dormant virus in later stages of life causes herpes zoster infection which may vary from subclinical infection to typical zoster, scattered vesicles, *zoster sine herpete* or disseminated zoster, which depends on the individual's immune status.
Case report: In this case series, we present two patients with herpes zoster involving the mandibular branch of the trigeminal nerve. Cytology revealed characteristic features of the infection including nuclear moulding, multinucleated giant cells and ballooning degeneration.
Conclusion: More recently, patients presenting with herpes zoster have been reported to have sub-clinical Covid-19 infection, suggesting a possibility that herpes zoster might be an indicator for latent Covid-19. Timely detection and treatment of this infection can reduce the risk of post herpetic neuralgia.

Keywords: **herpes zoster, cytology, multinucleated giant cells**

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INTRODUCTION

Varicella-zoster virus is a neurodermotrophic herpes virus that is pathogenic only to humans. Primary infection of the virus manifests as chickenpox. Herpes zoster is caused by reactivation of Varicella-zoster virus that remains dormant in the sensory root ganglia (post primary infection) (1). Individuals with suppressed cell-mediated immunity are at a higher risk of acquiring the disease (2). The lesions are characterized by pain along the affected dermatome followed by the appearance of multiple small vesicular rashes or pustules that rupture to form shallow ulcerations. Oral lesions commonly involve the trigeminal nerve and present on bound or movable mucosa accompanied by skin lesions overlying the affected quadrant (3). Around 22% of the infected individuals suffer from post-herpetic neuralgia (2). Unique changes in the cells infected by Varicella-zoster virus is evident using routine hematoxylin and eosin staining in cytopathology and histopathology. Here we report two such cases of Herpes zoster with typical features of the cell changes in Herpes zoster infection.

CASE REPORT 1

A 70-year-old male presented to our hospital complaining of ulcers in the mouth and difficulty in mouth opening for the past two days. The patient did not have any prodromal symptoms. Medical history and dental history were not contributory. On examination, multiple shallow ulcerations with erythematous borders were seen on the left side of the hard palate, confined to the midline (Figure 1). Clinical differential diagnosis included Herpes zoster and major aphthous stomatitis. Cytosmear prepared

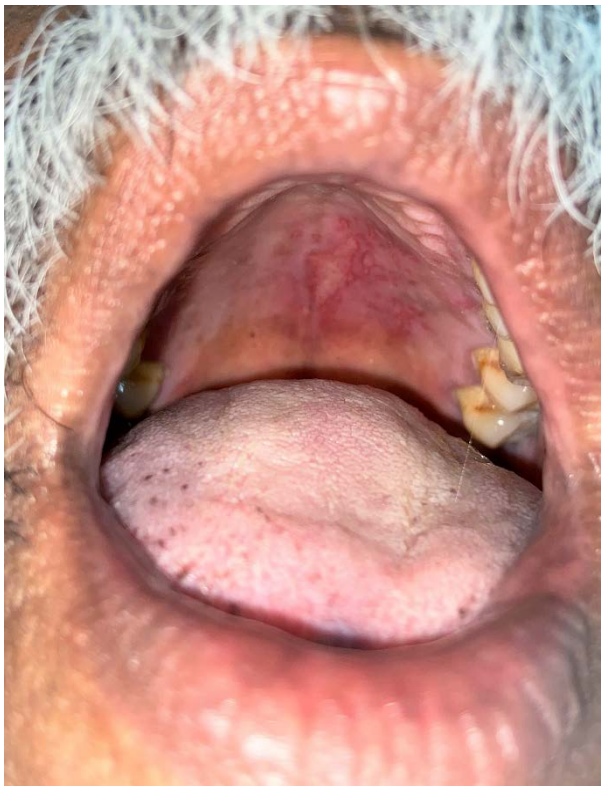


Figure 1. *Multiple shallow ulcerations with Erythematous borders on the left side of the hard palate confined to the midline*

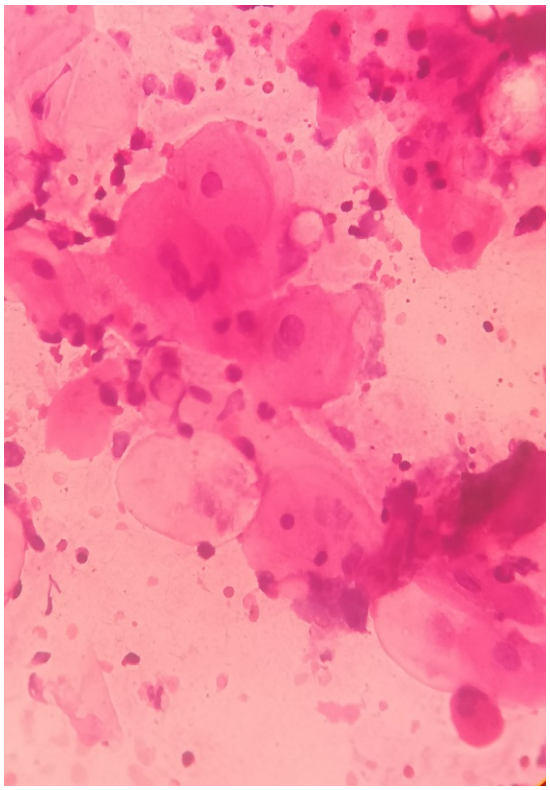


Figure 2. *Multinucleate giant cells with nuclear moulding*

from the ulcerations on the hard palate on hematoxylin and eosin staining showed epithelial cells in the background of mixed inflammatory cells. Multinucleate giant cells with nuclear moulding and fragmented nuclei were evident (Figure 2). Cytological features were suggestive of herpes infection. Correlating with the clinical features, the final diagnosis of Herpes zoster was given. The patient was prescribed acyclovir tablets for 7 days after which the lesion healed.

CASE REPORT 2

A 62-year-old male presented to our hospital with the chief complaint of rashes on the right side of

Figure 3. *Multiple crops of vesiculo-papular lesions on the right side of the face*

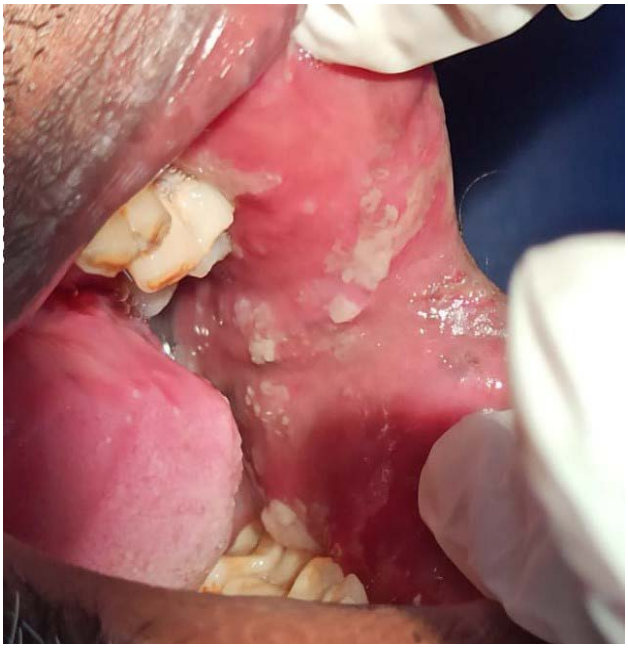
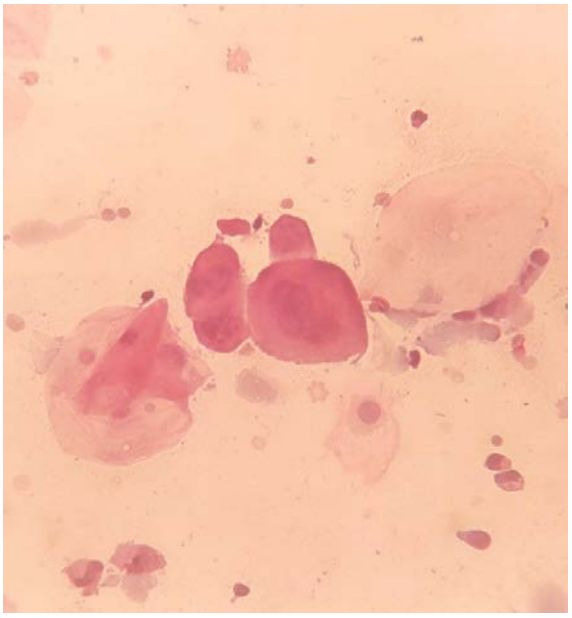


Figure 4. *Multiple small ulcers covered with slough*



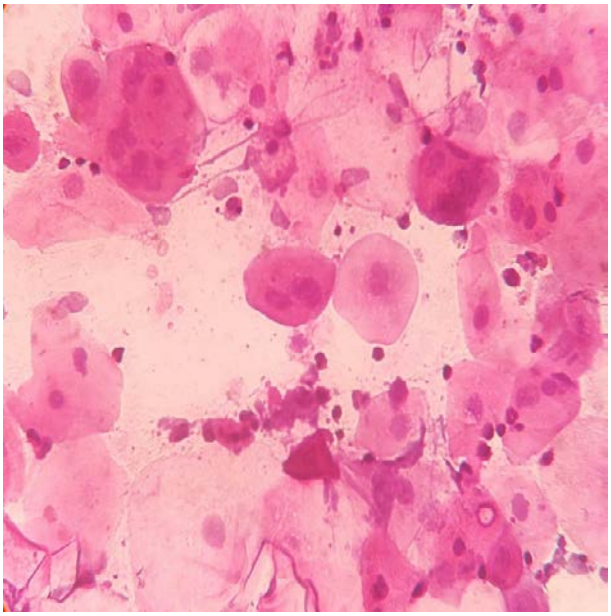


Figure 5. *and* **Figure 6.** *Moulding of squamous epithelial cells, forming multinucleate giant cells*

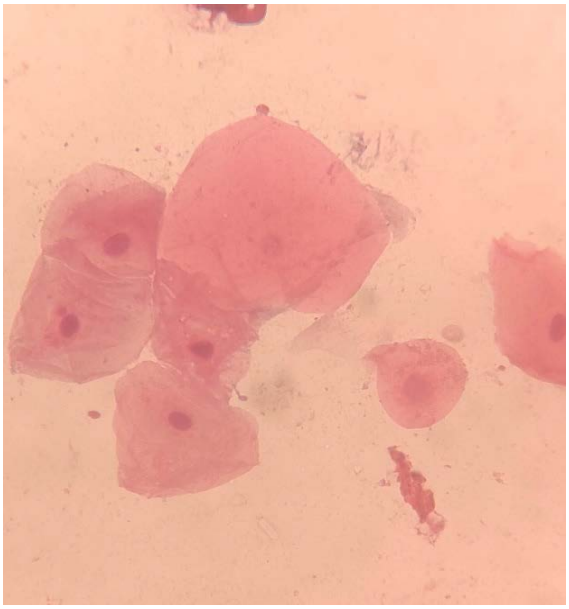


Figure 7. *Ballooning degeneration of epithelial cells*

the face associated with pain and difficulty in swallowing for the past two days. Medical history and dental history were not contributory except that the patient had undergone extraction two days before the appearance of rashes. On extraoral examination, multiple crops of vesiculo-papular lesions were seen on the right side of the face on malar, parasymphyseal and symphyseal region (Figure 3). Mouth opening was restricted. On intraoral examination, multiple small ulcers covered with slough were seen on the right lower lip, commissures, right buccal mucosa and the right side of the palate (Figure 4). A provisional diagnosis of erythema multiforme was given. Cytosmear prepared from the ulcers on hematoxylin and eosin staining showed moulding of squamous epithelial cells, forming multinucleate giant cells in the background of inflammatory cells (Figure 5). Ballooning degeneration of epithelial cells was also evident (Figure 6, Figure 7). The cytological features were characteristic of herpes infection. The final diagnosis of Herpes zoster infection was given in accordance with the clinical findings. The patient did not show for follow-up.

DISCUSSION

Varicella-zoster virus is the pathogen accountable for two most common human infectious diseases, chickenpox and Herpes zoster. Primary infection of Varicella-zoster causes chickenpox, primarily a childhood disease in non-vaccinated populations. In tropical countries like India, the infection is acquired in later stages of life, with adults being more susceptible to the disease. Due to late seroconversion, a relatively high proportion of women in child bearing age are infected by Varicella-zoster which may cause congenital Varicella syndrome in the foetus (4). The risk of mortality from Varicella-zoster infection is reported to be 23 - 29 times higher in adults (5). Varicella-zoster infection is contagious and disseminates through the blood stream. Post-primary infection or vaccination memory T cells specific to Varicella-zoster are activated and Varicella-zoster remains dormant in the sensory ganglia. Immunity against Varicella-zoster after infection lasts about 20 years. Over time, Varicella-zoster specific immunity lowers below the zoster threshold posing an increased risk for reinfection (2).

Reactivation of Varicella-zoster causes Varicella-zoster infection. Zoster or girdle refers to the segmental distribution of the disease (6). On reactivation, Varicella-zoster travels along the sensory afferents to the skin with hematogenous dissemination characterized by unilateral radicular pain and vesicular eruptions limited to the affected dermatome (7). Depending upon the patients' immunity, the presentation of Varicella-zoster infection may vary from subclinical infection to typical zoster, scattered vesicles, *zoster sine herpete* or disseminated zoster (8). Unilateral vesicular rashes and ulcers on the oral mucosa and skin overlying the affected quadrant, along the course of the trigeminal nerve

were evident in the cases reported here. Though the patients with Herpes zoster reported in this article were of older age, the disease was locally contained, limited to a single dermatome.

Varicella infection shows seasonal variation in tropical climates, with peak incidence in low temperatures and humidity (5). Similar presentation of Herpes zoster in the month of December (winter) was seen in the cases discussed in this article. Herpes zoster is commonly seen in later stages of life, as a reflection of the late primary infection. Suppressed cell-mediated immunity, drugs, HIV, malignancy, old age, stress and dental manipulation are some of the risk factors for the virus reactivation (3). However, about 90% of patients admitted with varicella are described as healthy or immune-competent (5), which is in compliance with the cases discussed in this article. Herpes-zoster enhances the chances of sensitization and deafferentation of the peripheral and central nervous system that may lead to post-herpetic neuralgia. Post-herpetic neuralgia persists for at least 1 - 3 years or longer, with the pain burden imposing a huge impact on the quality of patient's life (9). Early diagnosis and treatment of Herpes zoster reduces the risk of post-herpetic complications (2).

Laboratory diagnostic tests such as Tzanck smear, polymerase chain reaction (PCR), direct immunofluorescence assay (DFA), skin biopsy, and viral culture can be used to diagnose Herpes zoster. Cytology is characteristic for Varicella-zoster infection to identify the unique changes in the cells infected by Varicella-zoster. Stem and Longo in 1963 first observed that cytological changes in cells infected by Varicella-zoster could serve as potential markers in diagnosis (10). Multinucleate giant cells and Lipchitz bodies are the most characteristic feature of herpetic infection. Varicella zoster infection is not concurrent in all the cells, resulting in different phases of cellular change and inclusion material. Swollen/ballooned epithelial cell nuclei with margination of chromatin beneath the nuclear membrane is evident in the initial stages. Nuclear chromatin pattern and nucleolus are replaced by basophilic amorphous mass that give rise to the ground glass appearance. Multinucleate giant cells are formed by large syncytia of epithelial cells that may contain tight aggregate of up to 30 nuclei. Nuclear shape appears to be moulded by adjacent nuclei. Centrally placed intranuclear acidophilic material called Lipchitz bodies, surrounded by clear halo is seen in the last stages of formation (11, 12).

Solomon et al. compared Tzanck smear and viral isolation in Herpes zoster and reported that Varicella-zoster virus was recovered from vesicles in 78% of the patients with zoster who had a positive Tzanck preparation. The study implies 78% sensitivity of Tzanck smear in patients with Herpes zoster. Varicella zoster is less tolerant to transport and storage which attributes to the low recovery rate in viral cultures. Varicella-zoster proliferates *in vitro* at a slower rate and has a longer incubation period which makes it more prone to bacterial contamination. Therefore, Tzanck smear remains a simple and cost-effective method in diagnosing Herpes zoster infection (13).

More recently, patients presenting with Herpes zoster have been reported to have subclinical Covid-19 infection, suggesting a possibility that Herpes zoster might be an indicator for latent Covid-19 infection (14). This necessitates timely diagnosis, treatment and follow-up of the patients with Herpes zoster infection.

CONCLUSION

Herpes zoster is a painful blistering infectious disease with characteristic cytological changes that can be easily identified in smears. The likelihood of herpes zoster being a global health burden is also expected to increase as the population ages across the world. It is important to diagnose Herpes zoster as early as possible to prevent post-herpetic complications such as neuralgia.

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Kliničke i citopatološke karakteristike herpes zostera: prikaz dva slučaja

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SAŽETAK

Uvod. Varičela zoster virus je veoma infektivni α-herpes virus koji je patogen samo za humanu populaciju. Primarna infekcija varičela zoster virusa izaziva ovčje boginje, koje su zarazne i u Indiji prvenstveno inficiraju decu i adolescente. Nakon primarne infekcije, virus ostaje neaktivan u ganglijama korena senzora. Aktivacija "uspavanog" virusa u kasnijim fazama života izaziva herpes zoster infekciju, koja može da varira od subkliničke infekcije do tipičnog zostera, razuđenih vezikula, *zostera sine herpete* ili diseminovanog zostera, što zavisi od imuneta osobe.

Prikaz slučaja. U ovom radu prikazana su dva bolesnika sa herpes zosterom, kod kojih je zahvaćena mandibularna grana trigeminalnog nerva. Citologija je pokazala karakteristične osobine infekcije, uključujući nuklearni molding, multinuklearne džinovske ćelije i balonirajuću degeneraciju.

Zaključak. Nedavno je kod dva bolesnika sa herpes zosterom opisana subklinička kovid 19 infekcija, što ukazuje na to da herpes zoster može biti indikator latentnog kovida 19. Pravovremena detekcija i lečenje ove infekcije mogu smanjiti rizik od postherpetične neuralgije.

Klučne reči: **herpes zoster, citologija, multinuklearne džinovske ćelije**