INTRODUCTION

Herpes simplex virus (HSV) is a double-helix deoxyribonucleic acid (DNA) virus which contributes to different types of oral diseases. This virus is one out of nine types of the Herpesviridae family, that is, HSV-1 and −2, varicella zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus 6 and 7 (HHV-6A, −6B and −7), Epstein-Barr virus (EBV), and Kaposi’s sarcoma-associated herpesvirus (KSHV).

Globally, 70% of the population is detected with HSV shedding in their oral cavity. According to WHO, at least 90% of the world population has been infected by HSV. The data of HSV epidemiology in Indonesia are still limited. However, the study on global seroepidemiology showed that 70–80% adult population has been detected with HSV antibody. The average prevalence rate in children is 50% dan 76.5% for adults, with the age group of younger than 20 at 55.5%, followed by 20–39 years old group at 67.9%, and 87.5% of people older or equal to 40.

HSV infection can be latent or reactivate. The predisposing factors to cause remission are sunlight, emotional stress, immunosuppression, hormonal dysfunction, or neural trauma. The transmission can be passed through saliva, genital fluids, or organ transplantation.

Oral oropharyngeal lesions and recurrent blisters are commonly caused by HSV infection. This virus can cause a spectrum of diseases with various oral manifestations. Data published from Dr Hasan Sadikin General Hospital, Bandung, Indonesia, showed the percentage of HSV-1 infection in the inpatient unit were consisted of recurrent intraoral herpes (RIH), 9.43% herpes-associated erythema multiforme (HAEM), 3.77% labial herpes (LH), and 1.89% primary herpetic gingivostomatitis (PHGS), while in the outpatient unit were 85.71% RIH, and 14.29% LH. Furthermore, the contribution of HSV-1, −6, and −7 to OLP has been investigated as one of the predisposing factors as well.

Indeed, patients with primary HSV infection show a response to IgG and IgM antibodies. However, during the reactivation process, usually, only IgG is detected. Therefore, in recurring oral infections, serological examination of anti-HSV-1 IgG antibody is mandatory.

This report will discuss three patients with recurrent HSV-1 infection presented with different clinical diagnoses: the first was HAEM, then herpetic gingivostomatitis, recurrent intraoral herpes.
which after investigation showed a reactivation of herpesvirus infection (RIH), and the third was oral lichen planus (OLP) which was suspected of being predisposed by HSV-1. This case report aims to show distinct differences in the clinical features of recurrent oral HSV-1 infection cases with the same high level of IgG titer.

2 | CASE REPORT

The first case occurred in a 25-year-old man with painful recurrent canker sores on the upper and lower lips for two weeks, and he had difficulty while opening his mouth. The ulcers appear suddenly, preceded by fever. He came to a dentist and prescribed with plant-based topical antiinflammatory gel and antiseptic mouthwash. The patient admitted that he had experienced the same condition about two months ago and recovered spontaneously. He was suffering from end-stage renal disease, so he routinely underwent hemodialysis every two weeks for the last four years, had a history of hypertension, and routinely takes hypertension drugs. There were ulcerated lesions and serosanguinous crusting of the lips (Figure 1a and 1b), and erosive lesions of the lower labial mucosa (Figure 1c), but other intraoral conditions were difficult to assess due to minimal mouth opening. Involvement in other parts of the body was denied.

The symptoms and clinical features were leading to a diagnosis of suspected HAEM with erythema multiforme and herpes labialis as differential diagnoses. The patient was instructed to moisten his lips using a gauze with 0.2% chlorhexidine gluconate, then applied a thin layer of plant-based topical antiinflammatory gel, then with petroleum jelly three times a day. Patients were given information and education about the possible diseases he had and advised to eat high protein foods, vegetables, and fruits, and avoid spicy food and fries. Complete hematological examination and anti-HSV-1 IgG were performed to confirm the presence of HSV-1 infection.

Three days after the first visit, the patient felt less pain, and the serosanguinous crust on the lips was improved, but he still had difficulty while opening his mouth (Figure 2). The patient was taking the medication as instructed.

Laboratory examination results showed a decrease in hemoglobin, hematocrit, MCV, MHC, MCHC, bands, and segmented neutrophils, as well as an increase in red cell distribution width (RDW), monocytes, erythrocyte sedimentation rate (ESR), and IgG HSV-1 was very high reaching >200 U/mL. Based on these results, a clinical diagnosis of HAEM was determined. The patient was treated with 5% acyclovir cream applied to the lips five times a day, stopped using plant-based topical antiinflammatory gel, and continued using 0.2% chlorhexidine gluconate and petroleum jelly. Up to the reporting date, the patient had not come back to control.

The second case was a 23-year-old man who complained of discomfort on the right posterior of the palate in the past four days. The patient admitted that he had never experienced something similar before and had taken troches, clindamycin, and 3–5 tablets of prednisolone per day. The patient had a sore throat one week ago, high daily activities, increased stress, and drinking less water. Extraoral examination showed no abnormalities. Intraoral examination showed multiple ulcers with reddish borders, <1cm in diameter on the right posterior of the hard palate near teeth 16–17 (Figure 3a). There was an elongated fissure on the median dorsal of the tongue about 1–2 mm deep, covered with a white plaque membrane that can be scraped off, but does not leave erythematous tissue, and does not painful (Figure 3b). The clinical diagnosis of this patient was suspected herpetic gingivostomatitis of the right palate with a differential diagnosis of allergic stomatitis, fissured tongue (central longitudinal type), and coated tongue (Miyazaki score 3). The patient was prescribed with 0.1% triamcinolone acetonide in orabase cream and rinsed with 0.2% chlorhexidine gluconate three times a day, and a multivitamin once daily. We informed and educated the patient by direct communication regarding possible diagnoses, then he was advised to clean the teeth and tongue with a soft-bristled toothbrush, consume healthy foods, drink plenty of water at least eight glasses per day, take adequate rest, and avoid spicy food and fries. Patients were sent to get a complete hematological examination, anti-HSV-1 IgG, and IgE.

The patient was revisited after five days and admitted that the pain on the palate had reduced, only felt a slight sensitivity while resting. He took medications regularly but had not been using mouthwash at all. The lips were dry, but not exfoliative (Figure 4a). Intraorally, we can see that the ulcer on the right palate was regenerating/
healing (Figure 4b), while the condition of the tongue was still the same as the previous visit. The blood tests showed a decrease in the levels of bands leukocytes, and ESR, level of anti-HSV-1 IgG >200 U/mL, but IgE level was normal. The clinical diagnosis of this patient was cheilitis, and after obtaining the results from laboratory tests, the clinical diagnosis of the ulcerative lesion on the palate was RIH (in the process of healing), also longitudinal fissured tongue and coated tongue (Miyazaki score 3). The patient was prescribed with 200mg acyclovir tablets 5 times a day for two weeks, instructed to apply a thin layer of petroleum jelly five times a day, discontinued the use of 0.1% triamcinolone acetonide in orabase cream, continued the previous non-pharmacological instructions, and came back for one-week control.

On the third visit, the patient felt no pain and no new lesions were found. The patient took the medication regularly, but petroleum jelly was only used three times since the lips already moistened. Both extra and intraoral examination showed the lesion had healed. The lips were moist (Figure 5a), the ulcerated lesions on the hard palate had completely disappeared (Figure 5b), and the white membrane on the tongue had improved (Figure 5c). The patient was asked to follow a healthy diet, have enough drinks and rest, and always maintain good oral hygiene.

The third case was a 28-year-old woman who complained of asymptomatic white spots in her oral cavity and had recurred for the last two years. The patient was afraid if this is a sign of HIV infection, especially because her wedding day was around the corner. No history of recurrent ulcers and long-term use of medication was denied. There were no abnormalities on the extraoral examination, but we found multiple non-scrappable white plaques on the buccal mucosa, bilaterally, upper and lower labial mucosa, and the right dorsolateral of the tongue (Figure 6a-d). The clinical signs and symptoms refer to the diagnosis of suspected oral lichen planus associated with HSV-1 infection. The patient was instructed to maintain good oral hygiene, avoid spicy foods and foods with artificial seasoning. We refer her for routine hematology examinations and anti-HSV-1 IgG test, and anti-HIV screening as requested by the patient.

Three days after the initial visit, the complaint remained the same, only this time pinpointed ulcers appeared in the white patch location. Extraoral examination showed no abnormality, while on the intraoral we found multiple ulcers on the upper and lower lips, dorsolateral of the right and left tongue, and on the buccal mucosa bilaterally (Figure 7a-e). Serological examination showed a decrease in the bands and segmented neutrophils, as well as a very high level of IgG HSV-1 titer (199.8 U/mL). Anti-HIV was...
nonreactive. RIH was confirmed as the diagnosis. The patient was given 200mg acyclovir tablets five times a day and 1mg folic acid once a day for two weeks. To date, the patient has not returned to control.

Table 1 shows the results of serological tests in the three patients with IgG Anti-HSV-1 titer reaching more than 200 U/mL. This resulted confirmed the diagnosis and management of the disease. The patient was given acyclovir cream and tablets, and the condition showed an improvement during control.

3 | DISCUSSION

The HSV-1 life cycle begins with virion attachment and penetrates the epithelial or mucosal cell wall to the nucleus.3 The attachment process involves glycoproteins B (gB) and C (gC) of viruses that interact with hepatic sulfate proteoglycans (HSPGs). During the process of cell movement (motile), there is an elongation of actin-rich HSPGs filaments called filopodia.11,12 The HSV-1 virus travels (surfing) along the filopodia during the attachment process.12 Afterwards, these gene are expressed: immediate-early, early, and late genes, followed by DNA replication, nucleocapsid assembly, capsid maturation, envelope formation, then the new virus will be released (shedding) in the saliva, and dormant in the sensory nerves of the trigeminal ganglion.2,7,13

Immunosuppressive condition is among the factors that can reactivate HSV-1 infection.1,7 Primary infection and reactivation in immunocompromised patients as happened in our first case (history of kidney disease and hypertension) will involve many cells and have a greater risk of acyclovir resistance than the normal population.14

All three patients in this report experienced a reactivation of HSV-1 and presented with different clinical features as well as different clinical diagnoses. Table 2 briefly and clearly describes the differences of the clinical features, diagnosis, treatment, and follow-up condition.

HAEM is a hypersensitivity reaction predisposed by reactivation of HSV-1.15-17 HSV DNA is detected in 60% of recurrent HAEM patients.15 The pathogenesis of HAEM begins with the transport of viral DNA fragments through the peripheral blood circulation of CD34+ mononuclear cells (Langerhans cell precursors) to keratinocytes, thereby attracting HSV-specific CD4+ TH1 cells.15,17 In response to the HSV-1 antigen, an inflammatory cascade is triggered by interferon-γ (IFN-γ) from CD4+ cells resulting in epidermal damage.

Clinically, HAEM presents atypical/ multiforme lesions (ulcers, papules, pustules, or vesicles) on the skin or oral cavity (or both),15 and form a red-brown hemorrhagic crust especially on the lips16,18 as happened in case 1. Serosanguinous crusting is a characteristic feature of viral involvement, due to the shedding of the virus when plasma fluid is released and bleeding causing dry exudate, giving reddish-yellow crust features.16,18 (Figure 1a-c).

Figure 6 Case 3 on the 1st visit showed multiple white plaques that cannot be scraped off on the upper (a) and lower lip (b), right buccal mucosa and right dorsolateral of the tongue (c), and left buccal mucosa (d).

Figure 7 Case 3 during the 2nd visit. Multiple pinpoint ulcers were seen on the upper (a) and lower lips (b), lateral of the tongue (c), and right and left buccal mucosa (d, e).
Treatment choice for preventing recurrence of HAEM is oral acyclovir. The first patient was given 5% topical acyclovir, combined with an antiseptic to prevent secondary infection, and petroleum jelly to moisturize the crusting lips. The condition was actually improved on the next visit, but sadly, the patient was nonadherence. Given the self-limiting nature of HAEM, it is likely that within 2–6 weeks the lesion will heal, although there is still a possibility of recurrence.

The second and third patients were claimed to have a busy schedule and personal problems that cause stress. The third patient even anxiously thinks that she got HIV infection, especially prior to her wedding day. Aside from immunosuppressive conditions, stress is also one of the contributing factors in HSV-1 reactivation, which results in an increase in the concentration of HSV-1 titers and corticosterone (CORT) in plasma and ultimately causes latent conditions. Stress hormones will increase along with pituitary hormone axis (HPA) activity and immune system modulation. Stress-assisted immunomodulation (SAI) is an immune response to HSV reactivation caused by stress, whereas during acute and chronic stress, the body releases epinephrine, interleukins (IL-1, IL-6), Cyclic Adenosine Monophosphate (cAMP), glucocorticoids, and prostaglandins.

Initially, the second patient was diagnosed with herpetic gingivostomatitis due to the clinical presentation of multiple pinpoint ulcers found on the right palate (Figure 3a), and the patient admitted that he had never experienced the same condition before. However, after the anti-HSV-1 IgG test, the result showed a very high titer confirming a recurrence condition and altered the diagnosis of RIH. It is sensible that the patient developed PHGS in childhood so he could not recall it. We were then administered systemic acyclovir therapy, and the patient showed significant progress (Figure 5b). Moreover, the patient had good adherence, thus supporting the favorable outcome.

### Table 1: Serological examination results.

| Test               | 1st Case Male | 2nd Case Male | 3rd Case Female | Reference Value | Unit |
|--------------------|---------------|---------------|-----------------|-----------------|------|
| Hemoglobin         | 12            | 15.6          | 14.8            | 13.0–18.0       | g/dL |
| Erythrocytes       | 5.23          | 4.93          | 5.20            | 4.5–5.9         | 10^6/µL |
| Hematocrit         | 41^L          | 47            | 45              | 41–53           | %    |
| MCV                | 77^L          | 94            | 87              | 80–100          | fl   |
| MCH                | 22.9^L        | 32            | 28.5            | 26.0–34.0       | Pg   |
| MCHC               | 29.6^L        | 34            | 32.7            | 31.0–37.0       | %    |
| RDW                | 16.2^H        | 12.3          | 12.3            | 11.5–14.5       | %    |
| Leucocytes         | 5,850         | 6,400         | 5,820           | 4,400–11,300    | /µl  |
| WBC Count          |               |               |                 |                 |      |
| • Eosinophil       | 9             | 1             | 1               | 2–4             | %    |
| • Basophil         | 0             | 0             | 0               | 0–1             | %    |
| • Neutrophil Bands | 0^L           | 0^L           | 0^L             | 3–5             | %    |
| • Neutrophil       | 48^L          | 66            | 24^L            | 50–70           | %    |
| • Lymphocytes      | 29            | 27            | 68^H            | 25–40           | %    |
| • Monocytes        | 14^H          | 6             | 7               | 2–8             | %    |
| Sedimentation rate | 27^H          | 18^L          | -               | 0–15            | Mm/hour |
| IgG HSV−1          | >200^HH       | >200^HH       | 199.8^HH        | Negative <20    | U/mL |
| IgE Total          | -             | 56.3          | -               | <100            | IU/ml |
| Anti-HIV (screening)| -            | -             | Nonreactive: 0.07| Nonreactive <1 |     |
|                    |               |               | Reactive ≥1     | Reactive ≥1     |     |

Abbreviations: ^H, high; ^HH, very high; ^L, low; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; RDW, Red cell distribution width; WBC, White blood cells.
The third patient presented OLP-like symptoms and clinical features at the first visit (Figure 6a-d). Although there was no significant correlation between the clinical and histopathological features of OLP with HSV-1,22 evidently, anti-HSV-1 IgG titers increased in OLP patients and showed improvement after acyclovir administration.23 Nevertheless, ruptured vesicles were seen during the second visit (Figure 7a-e), which changed the diagnosis of RIH and the patients were treated accordingly. We also performed an HIV screening test by the patient’s request, and it was negative. Unfortunately, the patient still presumed that she was having an HIV infection and discontinued the consultation.

According to its life cycle, reactivated HSV will release viral progeny in the oral cavity, which is detected in HSV seropositive individuals.2 Although clinically asymptomatic, HSV-1 releases progeny in the oral cavity, both in acute and active recurrence states.2 Consequently, serologic testing is required to identify specific HSV-1 IgM and IgG antibodies to confirm a suspected history of HSV infection.15

IgM antibody levels increase on days 7–10 after the onset of the disease, then decrease and dissipate after several weeks or months, causing it undetected in the reactivation or reinfection process.24 Whereas, the IgG response occurs after IgM and remains in the circulation. IgG is an antibody with a large molecule, consisting of four polypeptide chains (two light chains and two identical heavy chains) with a shape resembling the letter Y and weighing about 150 kDa.25 Salivary IgG is the essential key of innate immunity in neutralizing HSV.2

While in the adaptive immune response, T helper CD4+ and T cytotoxic CD8+ T cells recognize HSV antigens (usually glycoproteins in the viral envelope), and by recognizing major histocompatibility complex (MHC) class I and II molecules, it will activate the B cell to produce antibody (Ig).2,24,25

During the primary HSV infection, HSV-1-specific IgA and IgM antibodies will be detected in the serum for a month. However, in the next one to five months, the levels of IgG antibodies will increase, while IgA and IgM antibodies will be decreased.7 This was in line with the high level of IgG in our patients.

The similarities and differences of the three cases presented in Tables 1 and 2 are addressed to help dentists to recognize the clinical features of recurrent HSV-1 infection with the same high level of Anti-HSV-1 titers that manifests as various diseases.

In conclusion, all three cases presented the clinical variability of recurrent oral HSV-1 infection, where the final diagnosis can be confirmed only by serological examination. The result of the serum IgG antibody test showed the same high value that indicates a recurrent infection.

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**CONFLICT OF INTEREST**
The authors declare that they have no competing interests.
AUTHOR CONTRIBUTIONS
All authors have contributed equally to the treatment and write this manuscript.

CONSENT STATEMENT
The patients were given consent to publish their condition for scientific purposes while keeping their identity confidential.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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