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Pseudomembranous candidiasis as an adverse effect of treating oral lichen planus with topical clobetasol

Grzybica rzekomobłoniasta jako powikłanie miejscowego leczenia liszaja płaskiego klobetazolem

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Abstract

Oral lichen planus (OLP) is a chronic inflammatory T cell mediated disease. Because the precise aetiology of this disease remains unknown, the treatment of OLP is focused on reducing symptoms, mainly through inhibiting the local inflammatory response. Topical corticosteroids with high potency are recommended as first choice medications for treating the symptomatic form of OLP. Treatment with topical corticosteroids is usually long-term or should be repeated when the acute symptoms of OLP recur, thus contributing to an increased frequency of adverse effects. Among them, secondary infection with Candida has been reported to occur in 12–30% of cases. Although antifungal drugs are sometimes additionally administered with topical steroids, which should help to prevent secondary oral candidiasis, the efficacy of such an approach has been recently questioned. Here, we present two cases of patients with erosive OLP treated with topical clobetasol that developed secondary acute pseudomembranous candidiasis during steroid treatment. We discuss treatment options and propose a clinical protocol that may be helpful in decision making for the treatment of OLP.

Keywords: oral lichen planus; topical corticosteroid treatment; pseudomembranous candidiasis.

Streszczenie

Liszaj płaski jamy ustnej jest przewlekłą, zapalną chorobą związaną z patologiczną aktywacją limfocytów T. Dokładna etiologia tego schorzenia pozostaje nieznana, dlatego leczenie liszaja płaskiego jamy ustnej sprowadza się do zmniejszania objawów, głównie wskutek hamowania miejscowej odpowiedzi immunologicznej. Miejscowe kortykosteroidy są często polecane jako leki pierwszego rzutu w objawowym leczeniu liszaja płaskiego. Miejscowe leczenie kortykosteroidami zazwyczaj jest przewlekłe lub powinno być powtarzane w momencie zaostrzenia objawów liszaja płaskiego, co może przyczyniać się do zwiększania częstotliwości efektów ubocznych, jak na przykład objawowa kandydoza, którą odnotowano w 12–30% przypadków. Pomimo że leki przeciwgrzybicze są czasami podawane razem z miejscowymi sterydami, co powinno pomóc w zapobieganiu wtórnej grzybicy jamy ustnej, skuteczność takiej terapii była ostatnio kwestionowana. W niniejszej pracy prezentujemy dwóch pacjentów z liszajem płaskim jamy ustnej, leczonych miejscowo klobetazolem, u których rozwinęła się ostra grzybica rzekomobłoniasta. Podejmujemy dyskusję na temat opcji leczenia i proponujemy protokół kliniczny, który może być pomocny podczas podejmowania decyzji w leczeniu liszaja płaskiego jamy ustnej.

Słowa kluczowe: liszaj płaski, leczenie miejscowymi sterydami, grzybica rzekomobłoniasta.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease affecting about 0.1–2.2% of the general population [1]. The etiology of this condition is complex, including genetic, environmental and immunological factors [2]. OLP usually presents as bilateral, symmetric lesions with a predilection to buccal mucosa, tongue and gingiva. OLP lesions are often asymptomatic, but in some patients, mainly those affected by the atrophic/erosive form, can cause symptoms ranging from a burning sensation to severe pain, sometimes interfering with speaking and eating, especially acidic or spicy food [1, 3]. Because the precise etiology of this disease remains unknown, the treatment of OLP is focused on reducing symptoms, mainly through inhibiting the local inflammatory response. Topical corticosteroids are recommended as first choice medications for the treatment of OLP, and among them clobetasol propionate, a corticosteroid with high potency, has proved to be the most effective in significantly reducing the extent of the lesions and improving the symptoms of OLP [4, 5]. Typically, OLP treatment with topical corticosteroids lasts for several weeks/months and in the majority of cases should be repeated when the acute symptoms of OLP recur, thus contributing to an increased frequency of adverse effects. Among

them secondary infection with Candida has been reported to occur in 12–30% of cases [4, 6]. To prevent oral candidiasis, a consequence of the local immunosuppressive effect of corticosteroids, an adjunct prophylactic antifungal treatment is sometimes proposed; however, no uniform therapeutic protocol is available [7]. Moreover, the available data are inconsistent, showing both positive effects for antifungal drugs in preventing oral candidiasis during topical steroid treatment with or without additional improvement in the efficacy of steroidal treatment [8], as well as no effect for such a preventive approach and the development of candidiasis during concurrent use of corticosteroid and antifungal drugs [7].

Here we report two cases of corticosteroid treated OLP patients that developed acute pseudomembranous candidiasis, and propose possible preventive and therapeutic strategies.

Case report

Patient 1

A 69-year-old male was referred to the Department of Periodontology and Oral Mucosal Diseases, Medical University of Lodz in March 2015 with lesions on the buccal mucosa. Patient reported persistent lesions over last 14 months. Examination of the oral cavity revealed white striae with erythematous area bilaterally on the buccal mucosa of approximate size 1.0x0.7 cm and 0.9x0.5 cm. The patient complained on burning and pain during eating. Dental examination also revealed tooth decay, chronic periodontitis and bad oral hygiene. The patient suffered from hypertension and cystic kidneys. He took following medications: metoprolol, indapamide, haloperidol, atorvastatin, levothyroxine, ramipril, tamsulosin, captopril and acetylsalicylic acid. Patient was a former smoker. The patient has been treated by dermatologist with ointments which included antibacterial, anti-inflammatory, antiallergic and antifungal components without any improvement.

On the basis of clinical examination atrophic lichen planus of the buccal mucosa have been diagnosed. The patient was advised to apply 0.05% clobetasol ointment on the buccal mucosa 3 times a day. During recall after 3 weeks patient still complained on burning sensation and pain of the oral mucosa. At examination, white, soft lesions similar to sour milk were detected on the palatal and the buccal mucosa (**Figure 1 a, b, c**). The lesions were loosely attached and could be removed by spatula leaving erythematous and bleeding basis. Pseudomembranous candidiasis has been diagnosed as a side effect of topical treatment with clobetasol propionate. The patient has been advised to use topically nystatin suspension 4 times a day. A subsequent visit took place after 2 weeks revealing overall resolve on candidal infection (**Figure 2 a, b, c**). Treatment with nystatin suspension was continued for the next 2 weeks. On recall, 2 weeks and 3 months later, asymptomatic reticular OLP lesions on the buccal mucosa and the absence of Pseudomembranous candidiasis have been demonstrated (**Figure 3 a, b, c**).

Patient 2

A 65-year-old female was referred to the Department of Periodontology and Oral Mucosal Diseases, Medical University of Lodz in June 2015 with painful lesions in the oral cavity. The patient complained on the presence of painful lesions on the buccal mucosa and tongue, as well as dry mouth since 5 years. Medical examination demonstrated the presence of white striae and erosions on the buccal mucosa and ventral side of the tongue. General history revealed that the patient suffered from polycythemia vera, gastritis and enlarged liver. She took hydroxycarbamide.

On the basis of history and clinical examination erosive oral lichen planus has been diagnosed. The patient was recommended to apply topically 0.05% clobetasol ointment on the buccal mucosa and additionally nystatin suspension 3 times a day as a preventive therapy. On recall 1 month later, the patient did not report any relief of pain and discomfort, and multiple white, soft lesions typical for pseudomembranous candidiasis were present in the oral cavity (**Figure 4 a, b, c, d**). It was recommended to discontinue clobetasol and nystatin, and start to apply topically miconazole in gel 4 times a day. After 2 weeks an improvement was noticed (**Figure 5 a, b, c, d**), and the patient was urged to continue topical application of miconazole gel for next 2 weeks. Subsequent recalls revealed that pseudomembranous candidiasis was successfully treated, while reticular OLP on the buccal mucosa and plaque-like OLP on the tip and ventral part of the tongue were still present (**Figure 6 a, b, c, d**). The patient still complained about dry mouth. Patient was recommended to apply topically antifungal and anti-inflammatory ointment. On recall one month later no relapse of pseudomembranous candidiasis has been noticed, while reticular OLP on the buccal mucosa and plaque-like OLP on the tip of tongue were still present. The patient reported overall improvement of subjective symptoms.

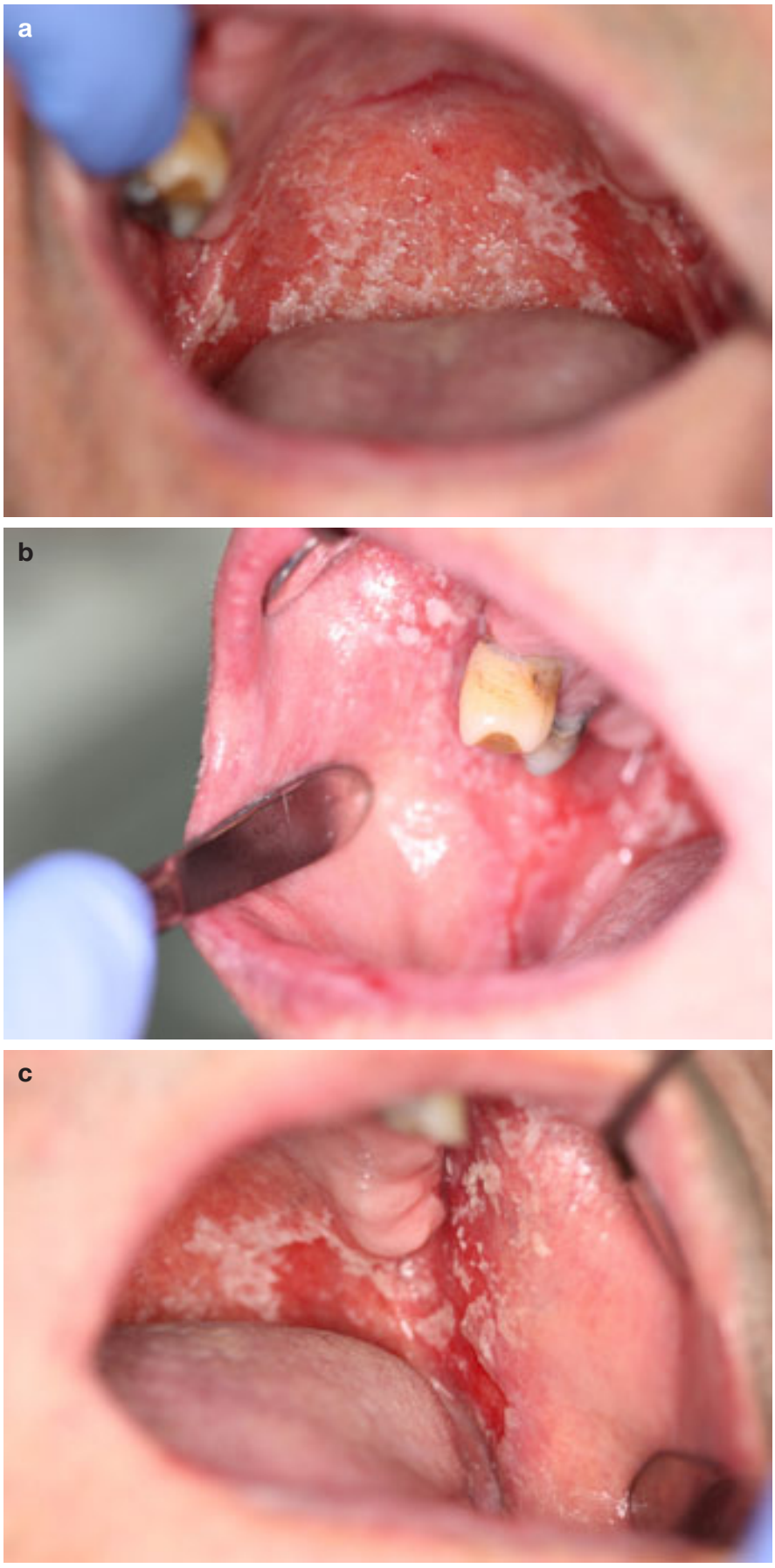

Figure 1. Pseudomembranous candidiasis as a complication after 3-week treatment of OLP with topical clobetasol. (a) palatal mucosa; (b) right buccal mucosa; (c) left buccal mucosa

Rycina 1. *Grzybica rzekomobłoniasta jako powikłanie trzytygodniowego leczenia OLP z miejscowym zastosowaniem clobetasolu. (a) błona śluzowa podniebienia; (b) błona śluzowa prawego policzka; (c) błona śluzowa lewego policzka*

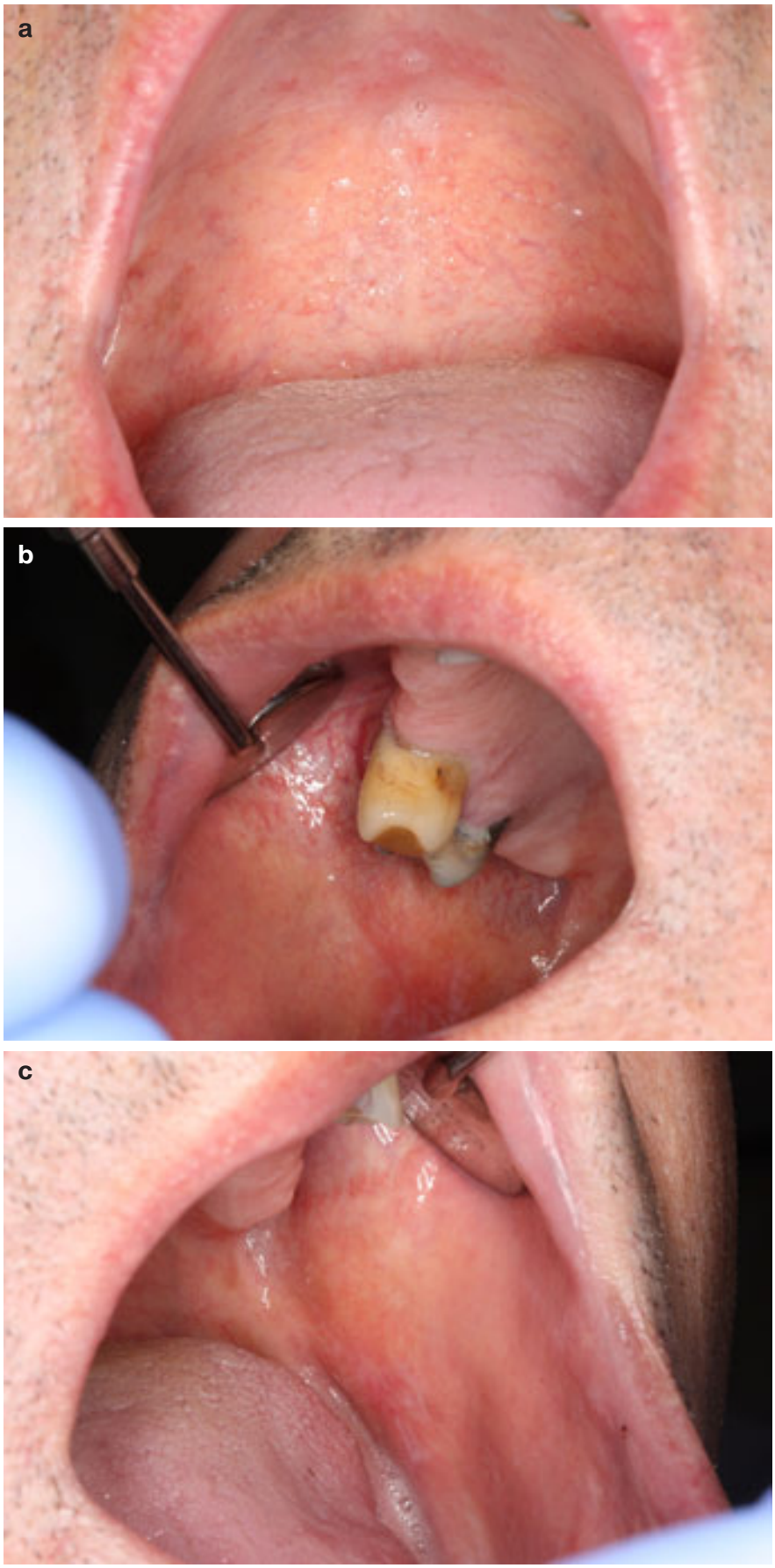

Figure 2. Complete resolution of pseudomembranous candidiasis lesions after 2-week treatment with nystatin and partial remission of OLP lesions. (a) palatal mucosa; (b) right buccal mucosa; (c) left buccal mucosa

Rycina 2. *Całkowite wyleczenie nacieków grzybicy rzekomobłonastej po dwóch tygodniach leczenia nystatyną i częściowe ustąpienie OLP (a) błona śluzowa podniebienia; (b) błona śluzowa prawego policzka; (c) błona śluzowa lewego policzka*

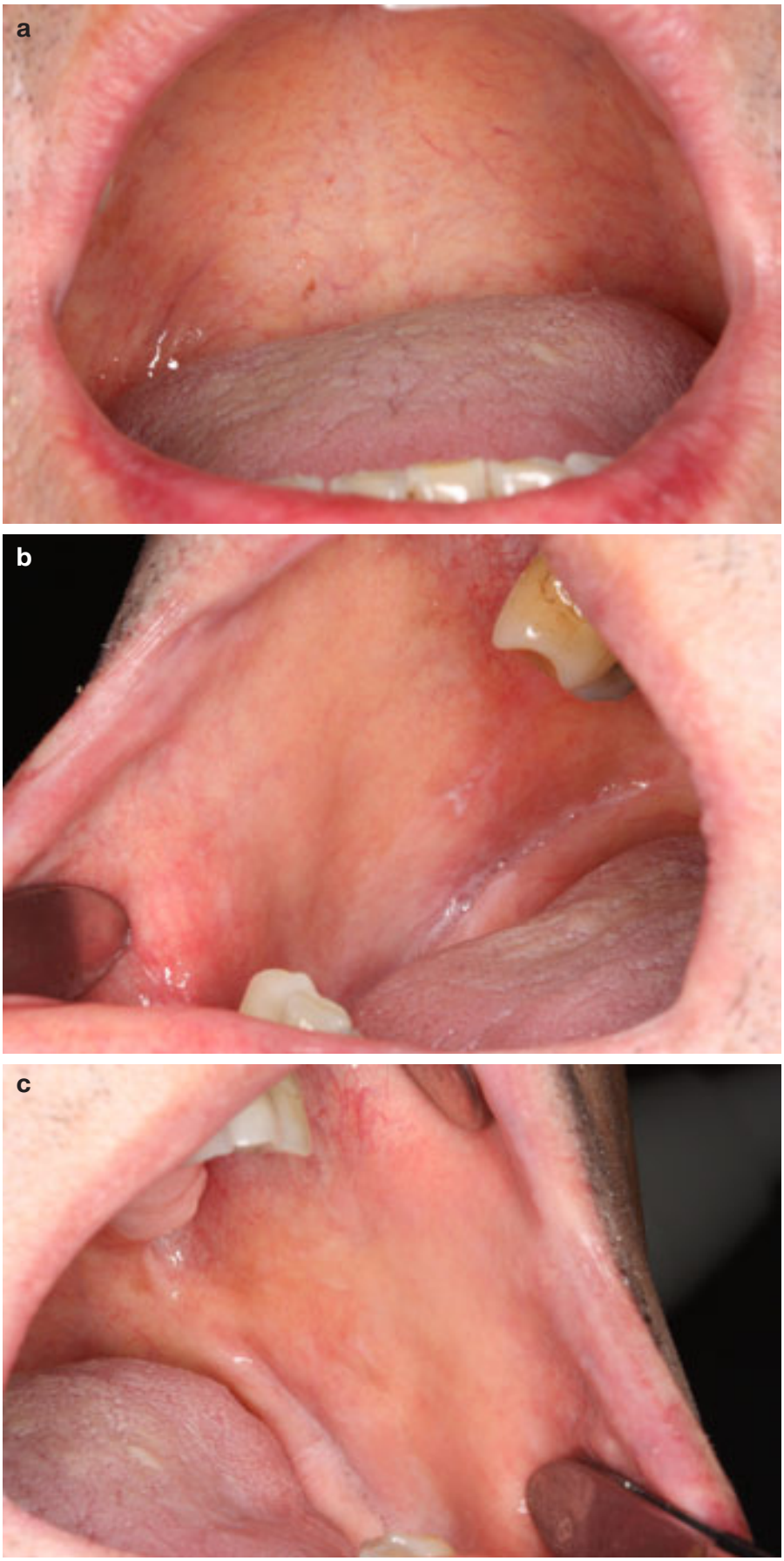

Figure 3. Absence of pseudomembranous candidiasis after 3 months. (a) palatal mucosa; (b) right buccal mucosa with small OLP lesion; (c) left buccal mucosa without OLP lesion

Rycina 3. *Brak grzybicy rzekomobłoniastej po trzech miesiącach. (a) błona śluzowa podniebienia; (b) błona śluzowa prawego policzka; (c) błona śluzowa lewego policzka*

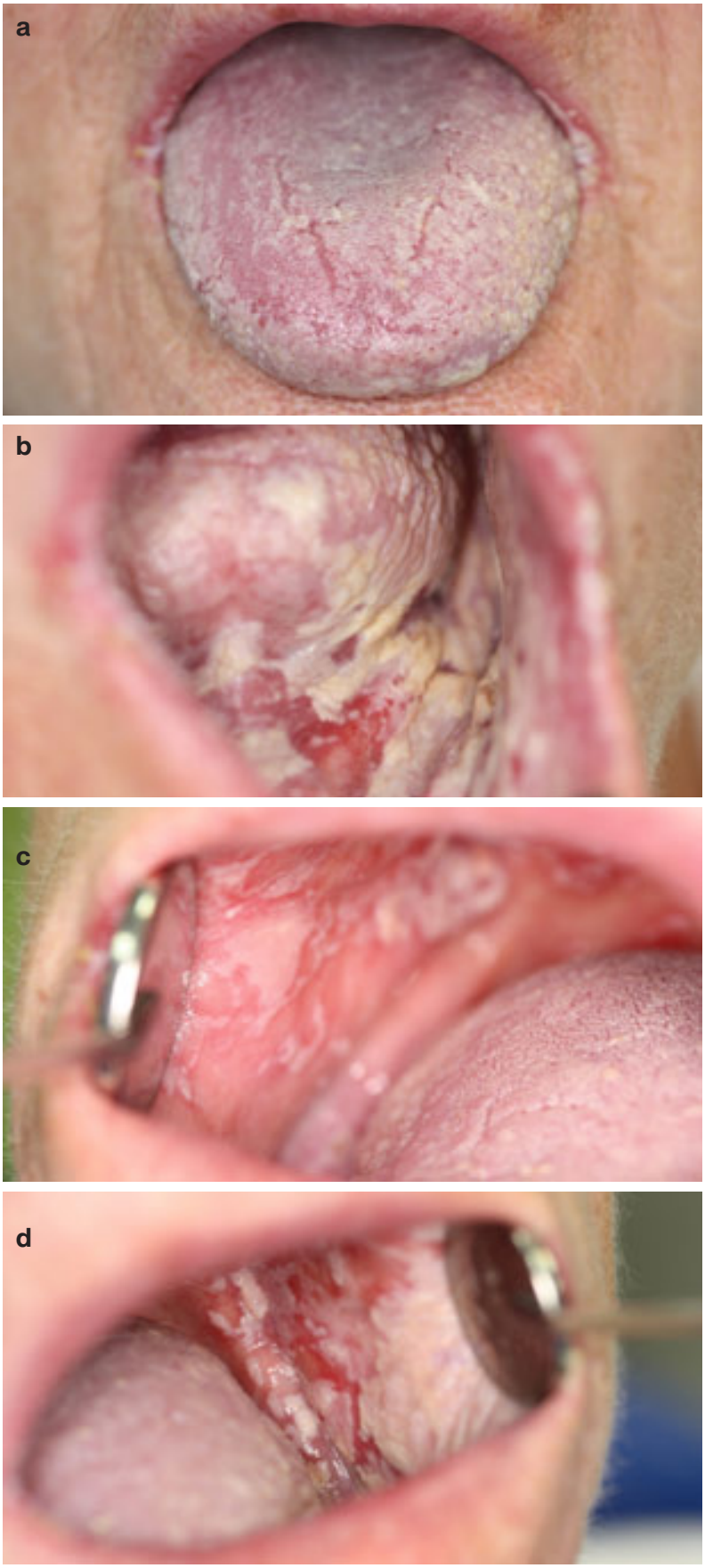

Figure 4. Pseudomembranous candidiasis as a complication after 4-week treatment of OLP with topical clobetasol with adjunct nystatin. (a) tongue; (b) ventral tongue, floor of the mouth; (c) right buccal mucosa; (d) left buccal mucosa

Rycina 4. *Grzybica rzekomobłoniasta jako komplikacja czterotygodniowego leczenia OLP z miejscowo stosowanym clobetasolem z nystatyną. (a) język; (b) brzuszna część języka i dno jamy ustnej; (c) błona śluzowa prawego policzka; (d) błona śluzowa lewego policzka*

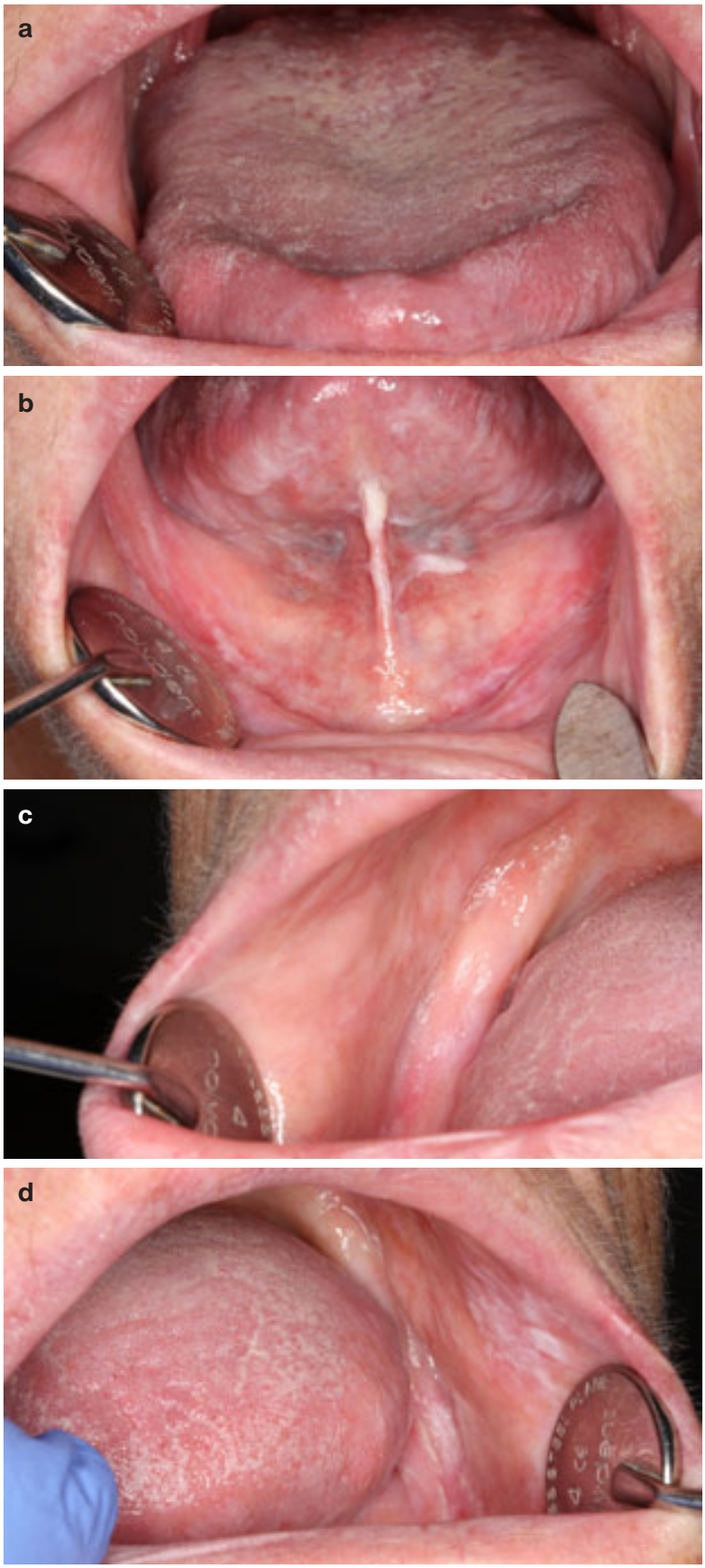

Figure 5. Improvement of pseudomembranous candidiasis after 2 weeks of treatment with topical miconazole. (a) tongue; (b) ventral tongue and floor of the mouth; (c) right buccal mucosa; (d) left buccal mucosa

Rycina 5. *Poprawa grzybicy rzekomobłoniastej po dwóch tygodniach leczenia miconazolem. (a) język; (b) brzuszna część języka i dno jamy ustnej; (c) błona śluzowa prawego policzka; (d) błona śluzowa lewego policzka*

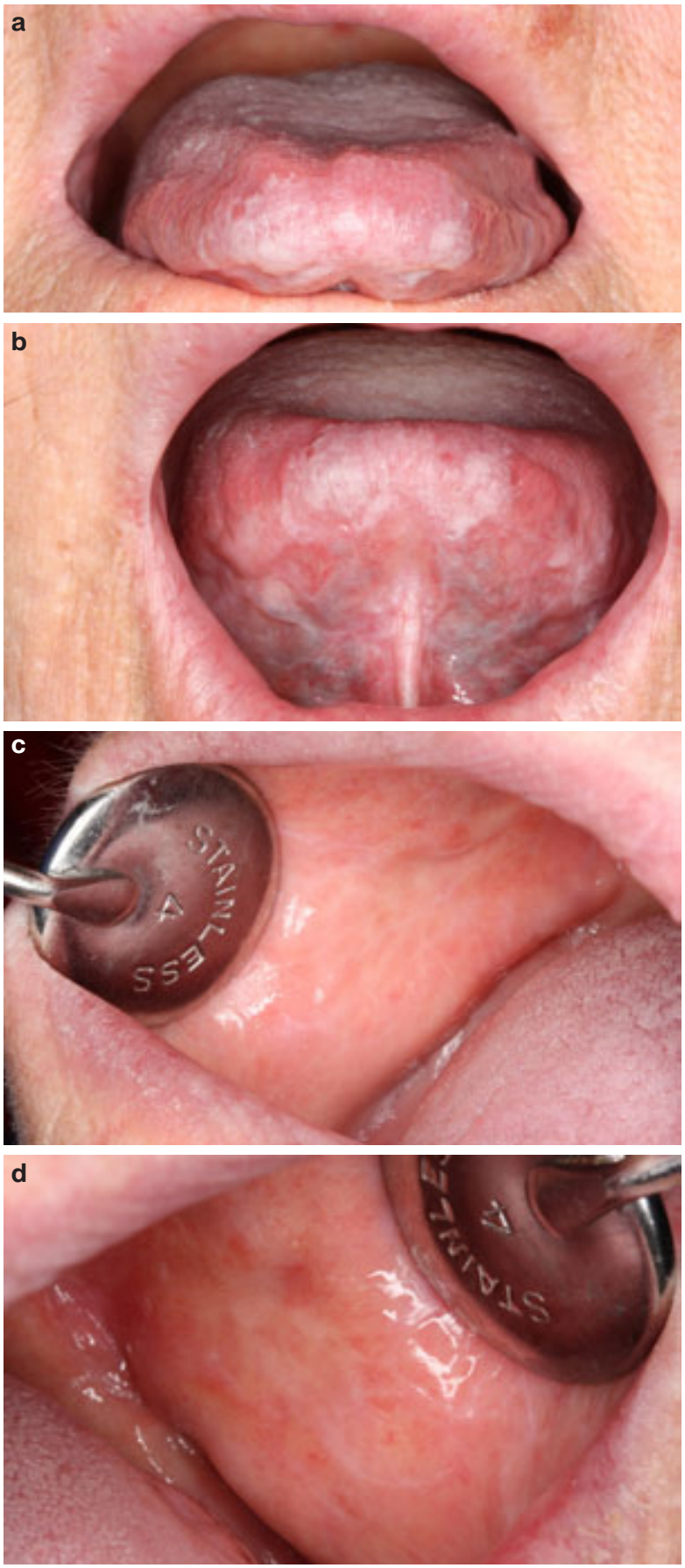

Figure 6. Partial deterioration of OLP on recall 2 months later. (a) tongue; (b) ventral tongue and floor of the mouth; (c) right buccal mucosa; (d) left buccal mucosa

Rycina 6. *Częściowe pogorszenie OLP obserwowane podczas wizyty 2 miesiące później. (a) język; (b) brzuszna część języka i dno jamy ustnej; (c) błona śluzowa prawego policzka; (d) błona śluzowa lewego policzka*

Discussion

Currently, topical corticosteroids are recommended as the first line treatment of symptoms associated with immune mediated diseases such as erosive lichen planus [9]. The beneficial effects of topical steroids for patients affected by OLP are consistent with the results documented by a number of clinical trials [8]. At present, topical corticosteroids seem to be safe when applied to oral mucous membranes with no serious side effects reported in the majority of examinations [10]. Comparable studies have demonstrated that clobetasol is able to reduce the extent of the lesions and improve the symptoms of OLP [8].

Candidiasis resulting from the overgrowth of normal oral flora by Candida spp. is a common side effect during topical corticosteroid treatment of oral mucosal diseases [11–16]. The use of inhalators with corticosteroids or overzealous use of antimicrobial mouthwashes might also increase the risk of developing oral candidiasis by suppressing local immunity and alterations in the oral flora [17, 18]. The oral carriage of candida organisms is reported to be 30–45% in a generally healthy adult population [19]. Asymptomatic colonization of the oral cavity by Candida spp. is frequently found in healthy individuals, and the detection of commensal yeasts is not indicative of infection [9], but it has been documented that prolonged steroid therapy can damage mucosal barriers promoting candidiasis [14, 20]. Age, medication use, and the wearing of dentures are the typical associated risk factors [18]. Recent research has shown an increase in the number of colonies of Candida spp., particularly C. albicans, detected after the first 7 days of topical corticotherapy in all the participants of the study, although clinical candidiasis was visible in only one of the examined subjects [9]. The prevalence of oral candidiasis following topical corticosteroid treatment might differ depending on the type of corticosteroid. For instance, it has been demonstrated that patients using clobetasol had a significantly higher incidence of oral candidiasis compared to betamethasone, dexamethasone or flucinonide [7].

Several studies showed that patients with OLP are more likely to harbor Candida spp., especially, patients with erosive or plaque-like OLP [7, 18, 21]. Further, it has been confirmed that Candida carriers are more likely to develop clinically relevant candidiasis compared to patients with negative Candida carriage [8]. Both patients presented here suffered from systemic diseases, and Patient 2 wore dentures. No clinical signs of candidiasis were visible at the baseline, but the patients were probably Candida carriers because even short term use of topical clobetasol resulted in symptomatic pseudomembranous candidiasis. Acute pseudomembranous candidiasis has been previously reported to be the most common form in patients with OLP treated with topical flucinolone acetonide [15].

Oral candidiasis can be effectively controlled or prevented in immunocompetent individuals by using antifungal therapy together with topical corticosteroids, which has been reported by many studies [4, 15, 16, 22]. However, different antifungal preventive strategies had different clinical outcomes. Among antifungal drugs, topical nystatin and miconazole were reported to effectively control Candida overgrowth [7, 8, 15]; while clotrimazol, chlorhexidine and probiotic yougurt had no beneficial effect [7]. Patient 1 had not received any antifungal medicine as a supportive therapy; while Patient 2 used nystatin, but on recall admitted to using it irregularly. Clinical symptoms of candidiasis might also occur in patients receiving azole containing antifungal therapy when non albicans species are overrepresented, like C. krusei, C. glabrata or C. dubliniensis [23, 24], thus culture and identification of Candida species and sensitivity profiles are warranted before starting treatment with topical steroids. Additional factors interfering with antifungl treatment are inadequate oral hygiene, xerostomia and systemic diseases (diabetes mellitus). Because of the chronic nature of OLP, a patient's medical history and possible drug interactions should be taken into account when considering treatment options. In addition, the time of application, size of the lesions, and the ulcerated area of the lesions may affect the emergence of complications [10].

In conclusion, to avoid the development of secondary candidiasis, different treatment strategies could be employed. Pretreatment or concurrent antifungal therapy could be recommended in Candida carriers or in patients with a greater risk of candidiasis (wearing dentures, xerostomia, and diabetes mellitus). The initial use of nystatin or miconazole is usually sufficient to control the symptoms of candidiasis. However, as steroid treatment in OLP patients can last for months or years, prolonged antifungal treatment may not be indicated. On the basis of the negative predictive value of Candida carriage, it is possible to avoid antifungal prophylaxis in patients that are Candida negative [9]. Thus, baseline assessment of Candida carriage is essential prior to initiating treatment. Another option is to use topical corticosteroids with lower potency for OLP treatment when it is possible, as the incidence of oral candidiasis is lower in patients treated with betamethasone, dexamethasone or flucinonide compared to clobetasol [7].

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Conflict of interest statement
The authors declare that there is no conflict of interest in the authorship or publication of contribution.

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