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Reviewing the use of imiquimod for molluscum contagiosum

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Abstract

We discuss imiquimod associated with non-application site mucosal reactions and two of our own clinical cases. In one of our patients, erosive cheilitis developed in a young boy after using topical imiquimod 5% cream for 5 nights weekly on bilateral cheeks, chin, and near vermillion border for molluscum contagiosum. The case is discussed with concerns for imiquimod use in molluscum contagiosum when used near mucosal surfaces.

Keywords: imiquimod, molluscum contagiosum, erosive cheilitis

Introduction

Molluscum contagiosum (MC) is a common childhood viral infection that is ultimately self-resolving. Untreated MC may last on average 6-18 months. Therapeutic interventions commonly used by dermatologists and primary care physicians are to (1) address symptoms such as pruritus or pain, (2) avoid comorbidities related to MC such as molluscum dermatitis, secondary infection, Gianotti-Crosti-like eruption, and Wells syndrome, (3) decrease possible autoinoculation to additional sites, and (4) improve cosmetic appearance. In-office destructive therapies, such as cryosurgery, curettage, needle/comedone instrument extraction, and cantharidin application, may be more effective than topical home treatments but may also incur potential side effects including pain, scarring, pigmentary alterations, and cost associated with multiple office visits. When destructive therapies or benign neglect are not chosen, topical therapies are often employed to hasten resolution. Topical therapies reported to be successful in treatment of MC include the following: tretinoin, adapelene, benzoyl peroxide, trichloroacetic acid, potassium hydroxide, povidone iodine, salicylic acid, and imiquimod.

Imiquimod (IMQ) is a toll-like receptor 7 agonist capable of immune modification via induction of interferon-alpha, a potent antiviral, at the application site [1]. It acts by stimulating an immune response via cytokines such as interferon-alpha, interferon-gamma, interleukin-12, interleukin-8, and tumor necrosis factor [1]. IMQ 5% cream is FDA approved for topical treatment of external genital warts (3 times weekly x 16 weeks), actinic keratosis (2 times weekly × 16 weeks), and superficial basal cell carcinoma (5 times weekly × 6 weeks), [1]. Off-label use of topical IMQ 5% cream has been reported to be used for MC successfully.

Topical IMQ 5% cream can be used for MC on most areas of the body with reported 33% to 77% complete clearance when used 3-5 times per week for 12 weeks [1]. In 2010, the safety and efficacy of IMQ 5% cream was compared to cryotherapy for MC in immunocompetent children aged 2 to 12 years old on the head and neck, extremities, trunk, and genitals [1]. Patients who received cryotherapy treatment showed a faster response, with 70% clearing in three weeks, as compared to IMQ but ultimately 8% of the patients treated with cryotherapy had a relapse within six months as compared to zero relapses with IMQ [1]. Although cryotherapy resulted in an apparently quicker

response with once weekly treatment, there were more relapses with cryotherapy as compared to imiquimod. This suggested IMQ may be a preferred treatment option based on its painless and home-based application method. However, application-site symptoms, such as erythema, itching, and burning have been recognized [1].

IMQ creates a localized immunologic response. Signs of local irritation include erythema, edema, induration, vesicles, erosions, ulcerations, and crusting [1]. The most frequently described application site symptoms were erythema (73%) and itching (76%) [1]. Approximately 10% of patients using IMQ will develop erosions and ulcerations at the application site [4]. Additionally, owing to the nature of the immune response, it is possible for adverse reactions to occur not only at the site of application, but anywhere in the vicinity of application [2]. However, predilection for mucosal reactions distant from application-site can be identified in the literature and is an important adverse effect of IMQ.

Although IMQ is known to cause direct reactions such as burning, itching, erosions, and ulcerations at the application site, aphthous ulcers have been noted outside the area of treatment [3]. These lesions are "painful shallow ulcers with a predilection for nonkeratinized areas, such as the buccal mucosa, the mucosal lip, ventral surface of the tongue, and soft palate" [2]. One case described a 28-year-old patient who applied IMQ to her cheeks, chin, and perioral region, but not on the lips and developed "painful and burning labial erythema and edema resulting in multiple fibrinous and crusty erosive plaques on her upper and lower lips" fifteen days into therapy [4]. The patient saw complete resolution with hydrocortisone acetate cream within one week [4]. Another case described a 21-year-old patient applying once daily IMQ for facial warts who, after one week, developed "multiple painful, partially confluent, aphthous-like ulcers" on her lower lip, resolving with twice daily topical clobetasol propionate after two weeks [3]. A pediatric case of a seven-year-old with verruca on the chin was reported who applied IMQ to chin without application to the oral mucosa and subsequently developed oral ulcerations after five days of daily IMQ, which resolved with mupirocin after one week [5].

Case Synopsis

A ten-year-old boy was seen in our office for approximately thirteen pink, shiny umbilicated papules scattered on bilateral cheeks and chin; additionally one was located close to the vermillion border of the right upper lip. He was diagnosed with MC and over the next several weeks, he was treated with two sessions of cryotherapy followed by at-home imiquimod 5% nightly for five days per week. Five weeks into his therapy, he was seen in office for erosions of the upper and lower lips (**Figure 1**). His mother had discontinued the imiquimod two days prior. She did use the cream on lesions located near the lips, but was not applying the cream directly to the lips. The patient was diagnosed with erosive cheilitis likely secondary to imiquimod and was advised to discontinue IMQ. Alclometasone 0.05% topical ointment was applied twice daily to the lips. At follow-up one week later, his lips were completely healed (**Figure 2**). We also had a case where a 2-year-old was prescribed IMQ 5% cream by his pediatrician for treatment of MC on forearms, abdomen, and thighs who developed a mucosal aphthous ulcer of

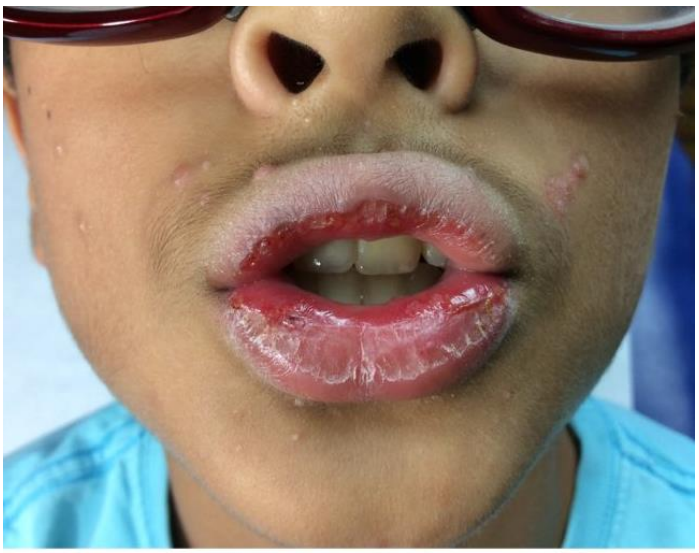

Figure 1. *Ten-year-old boy with erosive cheilitis that developed five weeks after nightly IMQ application 5 times weekly to lesions of molluscum contagiosum.*

the lower buccal mucosa 2 weeks into therapy. Parents were advised to discontinue IMQ and opted for treatment with cantharidin.

Discussion

Although most reports of ulcerations following use of IMQ are either at the site or general region of application, there have been "rare cases of paradoxical distant aphthous-like mucositis" [6]. For example, Maronas-Jimenez et al. described a woman in her third decade of life treated with IMQ for genital warts on the pubis. After three applications of the drug to the mons, she developed clusters of aphthous ulcer on the "inner area of both major labia, and two large ulcers with surrounding erythema and a grey-yellowish exudative surface, affecting the glands and the prepuce of clitoris, and submucosal portion of the right major labia" [6].

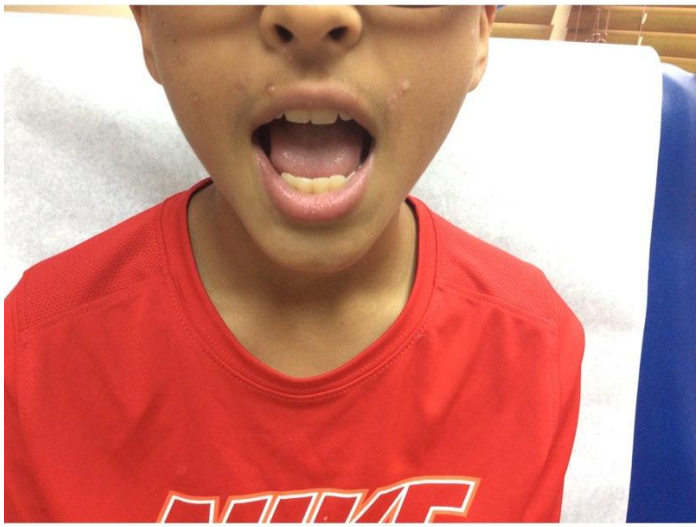

Figure 2. *Ten-year-old boy with resolved erosive cheilitis after one-week application of alclometasone 0.05% ointment twice daily.*

Moreover, IMQ efficacy and safety for treatment of MC in the pediatric population has yet to be firmly established. Dr. Kenneth A. Katz has written on this topic and directs attention to 2 RCTs conducted but never published by 3M, which are referred to in the product insert (PI), [7, 8]. The insert itself states that efficacy for MC failed to be demonstrated after 2 RCTs in which children aged 2-12 years old were compared after using IMQ 3 times weekly for up to 16 weeks versus vehicle-controlled patients [9]. The PI reviews outcomes at week 18 showing similarity between the IMQ-treated and vehicle-control groups with complete clearance seen in 24% (52 of the 217) versus 26% (28 of 106), respectively. Complete clearance in the second study was similar with IMQ-treated patients having 24% (60/253) success of complete clearance as compared to 28% (35/126) in the control group. Most importantly, systemic absorption, with possible leukopenia, is discussed as a risk in patients with single or multiple doses applied 3 times weekly for 4 weeks to at least 10% body surface area.

Possibly related to systemic absorption, febrile seizures in pediatric patients treated with IMQ have been reported. This is a conceivable adverse effect because of systemic absorption and cytokine stimulation. Although the authors believed it to be unrelated, one study of children using IMQ noted that 14% of their patient population developed fever [10]. This is important because another study by Mosher et al. reported a child who had been prescribed IMQ cream, one application per day, for MC on the abdomen and groin who developed significant erythema of the treatment area, dysuria, and intermittent fevers, which resulted in febrile seizures and hospitalization [11]. Whereas febrile seizures are usually without long-term implications of neurodevelopment [12], they are traumatizing for parents and important to consider in the spectrum of adverse effects of imiquimod therapy.

Conclusion

Although several modalities have been tried, molluscum contagiosum (MC) proves difficult to treat. The increasing side-effects of IMQ include mucositis, leukopenia, and imiquimod-induced vitiligo [13]. Our case provides another example that caution should be exercised when using imiquimod 5% cream, especially near mucosal surfaces. There is no uniformly accepted first-line therapy for patients with MC. Special considerations should be made based on the location of MC, number of lesions, age of the patient, skin type, and comorbidities (e.g. immunosuppression, atopic dermatitis)

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