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Concurrence of Stevens-Johnson Syndrome and Bilateral Parotitis after Minocycline Therapy

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Key Words
Stevens-Johnson syndrome · Parotitis · Minocycline

Abstract
Minocycline is an antibiotic of tetracycline derivatives that is commonly used in the treatment of moderate to severe acne vulgaris. It has been reported to cause rare adverse events from mild cutaneous eruption to severe forms including drug-induced lupus, serum sickness-like reaction, and hypersensitivity reactions, etc. The risks of adverse events attributed to minocycline have not been ascertained reliably and there are concerns about the safety of minocycline which could possibly result in life-threatening events such as the Stevens-Johnson syndrome. Here we demonstrate an unusual case of Stevens-Johnson syndrome in conjunction with bilateral parotitis after the intake of minocycline in a Korean boy suggesting discreet use of the drug.

Introduction

Minocycline is one of the most commonly used tetracycline derivatives for the treatment of acne vulgaris. Adverse drug reactions induced by minocycline include hyperpigmentation, autoimmune disorders (systemic lupus erythematosus), and hypersensitivity reactions (pneumonitis, serum sickness-like syndrome, hypersensitivity syndrome) [1]. Among these adverse reactions, both Stevens-Johnson syndrome (SJS) and parotitis are some of the rarest side effects caused by minocycline and the simultaneous occurrence of both diseases has not been reported yet. Herein we demonstrate an unusual case of SJS in conjunction with bilateral parotitis after the intake of minocycline in a Korean boy.

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Case Report

A 16-year-old Korean boy was hospitalized for multiple vesicles and bullae on erythematous bases on his face and trunk, and bilateral swellings in the region of the parotid glands. He had a two-month history of acne vulgaris. Seven days after taking oral minocycline 50 mg twice a day for his acne in the private clinic, he developed erythematous macular patches with a few vesicles and bilateral parotid swellings. He had not taken any other medication before starting minocycline therapy and that was his first cutaneous adverse event related to antibiotics, which he had not experienced before. Family, past and personal histories provided no significant information. He had been immunized with mumps vaccine at 16 months of age. Two days later he presented with a fever of 40.0°C, odynophagia, and conjunctivitis. Diffuse erosion of the oral mucosa and multiple purpuric macules with flat atypical targets were observed on the face and trunk (**fig. 1**a, b). Epidermal detachment on the body surface area reached approximately 10%. Bilateral swellings of parotid glands with pharyngeal injections exacerbated. Routine laboratory examinations revealed leukocytosis (19,000/mm^3), abnormal alkaline phosphatase (361 IU/l), and a markedly elevated serum-amylase level (826 IU/l). During the patient's illness, bacterial cultures from blood, urine and sputum revealed no evidence of a bacterial infection. Ultrasonographic examination of both cheeks showed small low echoic nodules with central hyperechoic fatty hilum in both parotid glands suggesting a bilateral parotitis with reactive lymphadenopathy. Histopathologic examination of the skin lesion showed diffuse necrotic epidermis with cleavage of the junctional zone and moderate infiltrations of mononuclear cells in the papillary dermis. The full-thickness necrotic epidermis detached from the dermis (**fig. 2**).

Even if histopathologic findings were compatible with both SJS and erythema multiforme major (EMM),they were more consistent with those of SJS in that dermal inflammation was moderate and a full-thickness epidermal necrosis and subepidermal detachment was much more pronounced [2]. The lesions of EMM principally occur in the papillary dermis which contains a dense mononuclear cell infiltrate [2]. Additionally, EMM is mainly caused by infection whereas SJS is chiefly induced by drugs. Our patient had no history of recurrent herpes simplex virus, upper respiratory infection, mycoplasma pneumonia or other infections which are firmly established as the major causes of EMM. No proof of bacterial infection was observed in his blood, urine and sputum, either. Clinically, brownish, flat blister lesions stood out on the trunk rather than the typical target features characteristically seen in EMM. Furthermore, the patient presented with bilateral parotid swelling usually regarded as a result of drug-induced hypersensitivity in contrast with unilateral swelling seen in the acute bacterial infection. Considering his not taking any medication but minocycline, we came to the conclusion that minocycline had played a decisive role in his illness.

Because the impression arose that SJS and parotitis were caused by minocycline, the drug was discontinued immediately and was replaced by systemic administration of prednisolone 15 mg twice a day, topical application of 0.25% desoxymethasone and 0.3% diflucortolone valerate, and wet dressing with aluminum acetate solution. The patient was given triamcinolone acetonide 40 ml via the intramuscular route for his odynophagia. After one week, buccal swelling and erosion of the oral mucosa regressed, and the serum-amylase level also decreased to the normal value. However, leukocyte count remained high until three weeks after the patient's skin lesions had started to improve with reepithelization. After four weeks, the skin lesions and the parotid swellings were completely resolved (fig. 1c). **Fig. 3** shows the sequence of events and the exposure to medication. The provocation test could not be conducted for safety reasons. There was no recurrence while the patient was followed up for two years.

Discussion

SJS is an acute, life-threatening mucocutaneous disease characterized by extensive necrosis and detachment of the epidermis [2]. According to Bastuji-Garin et al. [3], consensus classification was proposed: bullous erythema multiforme (EM), detachment below 10% of the body surface area plus localized 'typical targets' or 'raised atypical targets'; SJS, detachment below 10% of the body surface area plus widespread erythematous or purpuric macules or flat atypical targets. With respect to the above classification, the skin lesions of our patient were more consistent with SJS, so the diagnosis of SJS was made. The overall incidence of SJS was estimated at about 1 to 2 cases per million person-years [2]. SJS has been known to be induced by various drugs such as

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allopurinol, sulfonamides, barbiturates, etc., and a few cases, a.o. in Shoji et al. [4], 3 cases in a retrospective comparative study [1] and 3 cases in a multinational case-control study on SJS induced by minocycline in Europe [5] have been reported. The precise sequence of molecular and cellular events of SJS is incompletely understood; however, the immunologic pattern of early lesions suggests a cell-mediated cytotoxic reaction against keratinocytes leading to massive apoptosis [2]. It has also been suggested that minocycline is the only tetracycline which may lead to the formation of reactive metabolites acting as haptens [1]. Because only minocycline has a substitution of a dimethylamino group in the 7th position, its iminoquinone derivative may be a potential reactive electrophilic intermediate acting as haptens and induce a cell-mediated cytotoxic immune response in the epidermis and dermis [1].

The pathophysiology of SJS is still unclear. However, it is now established that drugs are the most important etiologic factors whereas most cases of EMM are related to infectious agents [2, 6]. More than 100 different drugs have been reported as possible causes including primarily alopurinol, sulfonamides, barbiturates, lamotrigine, phenytoin, oxicam NSAIDS and aminopenicillin [2]. Clinical experiences showed that causality of EM was linked with recurrent herpes simplex virus, mycoplasma pneumonia infection and other bacterial or viral infections. Drugs are a rare cause of EM with mucous membrane lesions [2, 6]. The lesions of SJS are primarily macular and blister lesions with flat or flaccid targets with widespread erythema in contrast with papular lesions with typical target features of EM [2, 6]. The histopathologic appearance of SJS lesions is different from that of EM in that dermal inflammation is moderate to absent, epidermal involvement rapidly evolves to a full-thickness epidermal necrosis and sub-epidermal detachment is much more pronounced [2, 6].

Parotitis is usually associated with mumps or other viral infections of the parotid glands. Viral or bacterial infection, endocrine disease, and drug medication can also potentially induce parotitis [7]. It is usually caused by the mechanical blockage of salivary ducts, resulting in reduced production of saliva, accompanied by a markedly elevated serum-amylase level, and tender, red cheeks. Drug-induced parotitis is a relatively uncommon adverse drug reaction [7]. Though the incidence of parotitis has dropped to a very low level, 0.8 in 100,000, due to vaccination, no case induced by minocycline has been reported yet. In general, it has signs of systemic involvement such as skin rash, conjunctivitis, hepatomegaly, pericarditis, or jaundice [7]. While viral or bacterial infection affects the parotid gland unilaterally, drug-induced parotitis features bilateral swellings of the parotid glands, with marked improvement following the cessation of the drug as shown in this case [7]. According to Speed and Spelman [8], all the patients with phenylbutazone-induced parotitis showed several signs of systemic involvement and all had bilateral parotitis. Iodines, phenylbutazone, oxybutazone, thioridazine, and tetracycline derivatives have also been associated with parotitis [7]. Vidal and González [9] reported that the administration of doxycycline 200 mg daily caused bilateral parotitis. It is not known how these drugs can cause parotitis, but hypersensitivity reactions are the most commonly mentioned cause [7]. Rarely, a few cases of parotitis caused by anticholinergics and antipsychotics have been reported. For example, Mirsky [10] described bilateral swellings of the parotid glands in a 75-year-old woman with rheumatoid arthritis after taking phenylbutazone 100 mg four times daily. In another case, Garfunkel et al. reported a 57-year-old woman who had been given a 5-day course of phenylbutazone 600 mg/day for several weeks [11]. She developed acute bilateral swellings of the parotid glands, accompanied by dry mouth, pain, fever, visual blurring, facial rash, and diffuse myalgia. Rosen described two cases of antipsychotic drug-induced parotitis [12].

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Minocycline is widely regarded as a successful antibiotic in the treatment of acne vulgaris, due to its clinical efficacy and easier dosing. Furthermore, because of its long half-life, minocycline generally has serum levels two to four times higher than other tetracycline derivatives, and thus needs to be taken only once or twice daily in a smaller dosage than tetracycline. However, the increasing number of case-reports on the adverse events suggests that minocycline has a greater risk of severe side-effects than other tetracyclines. Two studies were performed which provided the incidence of rare adverse events; the first found an overall incidence of 13.6% (95/700) [13], and the second suggested that minocycline was associated with an 8.5-fold increase of a lupus-like syndrome compared to 1.7 for other tetracyclines [14]. One retrospective review showed the increased frequency of serious adverse events caused by minocycline compared to other tetracyclines [1]. 19 cases of hypersensitivity syndrome reaction due to minocycline, 2 due to tetracycline, and 1 due to doxycycline were identified. 11 cases of serum sickness-like illness due to minocycline, 3 due to tetracycline, and 2 due to doxycycline were identified. All 33 cases of drug-induced lupus were attributable to minocycline [1]. However, no reliable overall evaluation of the relative risk of adverse effects of minocycline versus other tetracyclines has been made yet.

Along with the above findings, Mockenhaupt's study showed an up-to-date evaluation of the risk of recent marketed drugs to induce SJS or toxic epidermal necrolysis [5]. Though minocycline does not belong to the 'highly suspected' drugs, namely anti-infective sulfonamides, anti-epileptic drugs, oxicam-NSAIDs, and non-nucleoside anti-retroviral agents, the anti-epileptic drug lamotrigine, it was classified as 'significant but lower risk' drugs such as NSAIDS, macrolides, and cephalosporins [5]. 3 cases were identified to be induced by minocycline among 7 induced cases by tetracyclines [5].

Still, lack of number of case-control studies demands performing further large-scaled control studies with appropriate controls and reliable validity. For estimating the risk of minocycline, large-scaled case-control studies upon severe adverse events ought to be planned in an Asian market as well as American or European market. Although rare, it is worth noticing that minocycline can induce SJS and bilateral parotitis with systemic involvement at the same time and the case proves that cautious prescription of minocycline is required.

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Fig. 1. **a** Multiple brownish macules with flat atypical targets were observed on the face. **b** Multiple purpuric macules with flat atypical targets were observed on the back. **c** Four weeks after systemic corticosteroid medication. The bullous lesions and bilateral parotid swellings resolved with mild residual erythema.

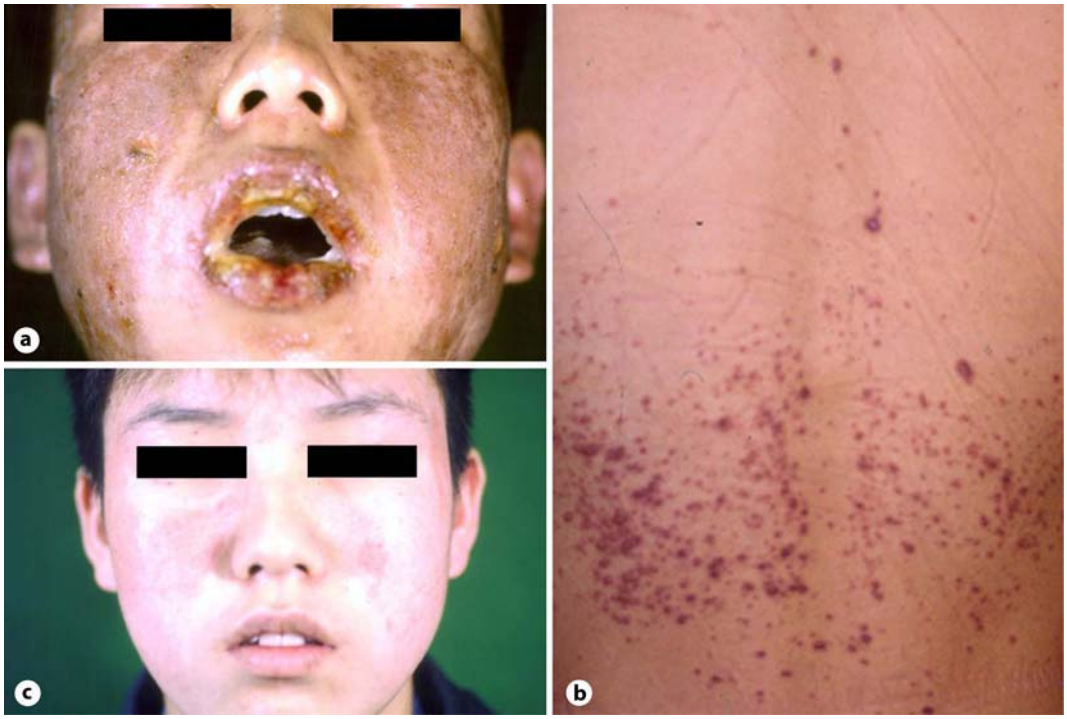

Fig. 2. Histopathologic examination showed diffuse necrotic epidermis with cleavage of the junctional zone and moderate infiltrations of mononuclear cells in the papillary dermis. The full-thickness necrotic epidermis detached from the dermis (HE, ×40).

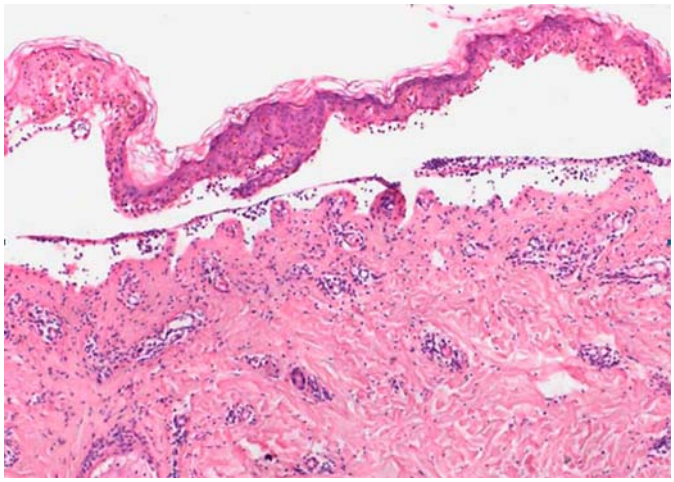

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Fig. 3. The flow chart shows the sequence of events and the exposure to medications.

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