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Staphylococcal scarlet fever associated with staphylococcal enterotoxin M in an elderly patient

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ABSTRACT

Staphylococcal scarlet fever (SSF) is characterized by an exanthem without enanthem, bullae, or exfoliation, and is known to be related to *Staphylococcus aureus* toxins, especially superantigens. It has been reported in children and young adults. Herein, we report the first case of an elderly patient with SSF caused by staphylococcal enterotoxin M (SEM), associated with otitis externa. The patient presented with maculopapular rashes on both arms, thighs, and abdomen and with erythroderma on the face, ears, neck, chest, and back, all of which was followed by desquamation on the face, ears, and trunk. A culture of ear discharge grew methicillin susceptible *S. aureus* that was only positive for SEM among the superantigens tested.

Introduction

Staphylococcus aureus produces numerous toxins, resulting in toxin-mediated diseases such as staphylococcal toxic shock syndrome (TSS), staphylococcal scalded skin syndrome (SSSS), and staphylococcal foodborne diseases (Grumann et al., 2014).

Staphylococcal scarlet fever (SSF) is characterized by an exanthem without enanthem, bullae, or exfoliation, and it is considered to be a mild form of SSSS or TSS (Courjon et al., 2013; Lo et al., 2009). SSF has never been reported in elderly patients, and an association between SSF and staphylococcal enterotoxin M (SEM) has not been published previously (Courjon et al., 2013; Lina et al., 1997; Lo et al., 2009; Wang et al., 2004; Weisse, 2001). Thus, to our knowledge, we report the first case of an elderly patient with SSF caused by SEM, which was associated with a case of otitis externa.

Case report

A 74-year-old man visited an emergency room because of a fever and rash that continued for about a week. He reported that the rash initially appeared on both upper arms and then spread throughout his whole body. He denied taking any other medication except drugs for hypertension and diabetes mellitus. Two years ago, he had been treated for tuberculous empyema for a year. Three months ago, he underwent a laparoscopic cholecystectomy for gallbladder cancer. He denied partaking in any specific outdoor activities where he might have encountered the pathogen.

The patient's initial vitals were: blood pressure = 109/64 mm Hg, pulse rate = 99 beats/ minute, respiratory rate = 18 breaths/ minute, and temperature =39.3 °C. He had maculopapular rashes on both arms, thighs, and abdomen (Figure 1). He also had diffuse erythroderma on his face, neck, ears, chest, and back without itching or tenderness. He did not complain of otalgia, but whitish discharge and patches were identified in his right ear canal. The tympanic membranes, tonsils, tongue, and oral mucosa were all normal. His white blood cell counts were 8,890/mm^3, hemoglobin level 10.5 g/dL, platelet counts 137,000/mm^3, and erythrocyte sedimentation rate was 36 mm/hour (normal range $\leq$ 27 mm/hour), CRP 7.78 mg/dL (normal range $\leq$ 0.5 mg/dL). Chest CT scan revealed no significant change in chronic empyema of the right pleura. Abdomen CT scan showed only mild splenomegaly.

Intravenous ceftriaxone (2 g) once daily and 100 mg of oral doxycycline twice daily were empirically administered to treat possible rickettsial disease and severe leptospirosis, considering the seasonality of those diseases in Korea. Topical ofloxacin was administered to treat the patient's otitis externa. The patient became afebrile and desquamation on his face, ears and trunk was identified on the fourth day of hospitalization. On the fifth day, the patient's skin had almost normalized. Blood cultures did not grow any pathogens, but ear discharge culture grew *S. aureus*. The antibiotics were stopped after diagnosis of SSF on the sixth day of hospitalization, when his symptoms resolved completely. Thereafter, serum *M. pneumoniae* antibody IgM, antibodies against *Orientia tsutsugamushi*, *Leptospira*, *Anaplasma*, Hantaan virus, and PCR for severe fever with thrombocytopenia syndrome virus were all negative except for *M. pneumonia* total antibody, which yielded a 1:320 titer.

In vitro antimicrobial susceptibility testing for an *S. aureus* isolate was performed by the broth microdilution method according to the Clinical and Laboratory Standards Institute guidelines. The isolate was resistant to penicillin-G, but was susceptible to oxacillin and vancomycin. Toxin gene presence (Supplementary material, Table S1) was determined by PCR amplification. Briefly, genomic DNA from the isolate was extracted

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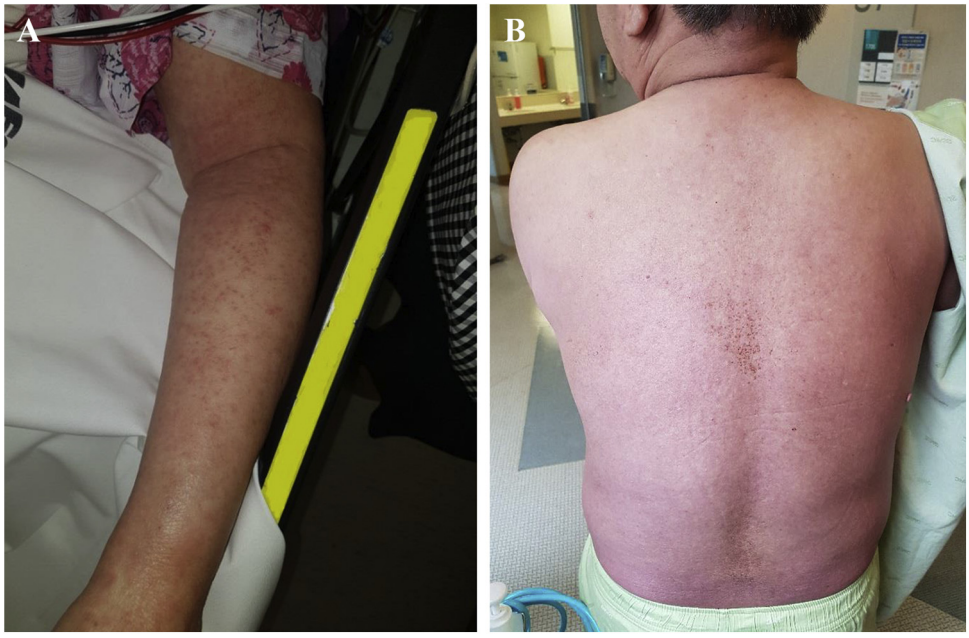

Figure 1. The patient presented with a maculopapular rash on the left arm (A) and diffuse erythroderma on the back (B).

by using the G-spin genomic DNA extraction mini kit (iNtRON Biotechnology, Korea) according to the manufacturer's instructions. The primer sets used to detect toxin genes were those previously described (Chiang et al., 2008; Jarraud et al., 2002; Yamaguchi et al., 2002). PCR was performed under the following conditions: an initial 5 min denaturation step at 94 °C; followed by 30 cycles of amplification (denaturation at 94 °C for 30 s, annealing at 55 °C, 30 s, and an extension at 72 °C for 1 min) and a final extension at 72 °C for 7 min. The PCR product was verified by gel electrophoresis and confirmed by DNA sequencing. The isolate produced SEM and delta and gamma hemolysin components A, B, and C. Toxic shock syndrome toxin (TSST)-1, other staphylococcal enterotoxins (SEs), and exfoliative toxin (ET) A and B genes were not detected. To investigate the genotype of the isolate, multilocus sequence typing (MLST) was carried out by PCR amplification and sequencing of seven housekeeping genes (Supplementary material, Table S2) (Enright et al., 2000). An allelic profile and sequence type were assigned using the online *S. aureus* MLST database (http://saureus.mlst.net/). Staphylococcal protein A (*spa*) typing was performed (Harmsen et al., 2003), and the *spa* type was determined using the Ridom SpaServer (http://spaserver2.ridom.de/spatypes.shtml). To identify a different accessory gene regulator (*agr*) allele, *agr* typing was performed (Jarraud et al., 2002). Further molecular typing of the isolate categorized it as ST89 and revealed that it carried *spa* type t375 showing *agr* group III.

Discussion

SSF was first proposed in 1900, and was resurrected as a disease entity that is caused by epidermolytic toxin-producing staphylococci (Weisse, 2001). However, most isolates from SSF cases were negative for ETs but positive for TSST-1 and other SEs; thus, SSF was thought to conform better to diagnoses of abortive forms of TSS, rather than a mild form of SSSS (Lina et al., 1997). The authors also suggested that SSF was associated with desquamation with no exfoliation during the recovery phase, similar to TSS. Our patient had a generalized maculopapular rash on his extremities and abdomen that was similar to rashes associated with scarlet fever, and he had TSS-like erythroderma followed by mild desquamation on the face, ears, and trunk.

A recent study attempted to differentiate these vague mild forms of *S. aureus* toxin-mediated disease according to toxin encoding genes and skin findings (Courjon et al., 2013). They classified them into an exfoliation-associated rash and a superantigen-associated rash. Compared with an exfoliation-associated rash, a superantigen-associated rash most prominently occurred along the trunk, with no involvement of skin folds, and there was an absence of Nikolski sign.

S. aureus encodes numerous toxins, including pore-forming toxins, ETs, and superantigens (Grumann et al., 2014). The identified SSF-associated toxins are primarily superantigens, including SEA-D, SEG, SEI, TSST-1, and rarely, ETA and ETB (Courjon et al., 2013; Jarraud et al., 1999; Lina et al., 1997; Lo et al., 2009; Wang et al., 2004). The isolate from our case was only positive for SEM among the superantigens. In previous studies, SEM was not reported to have an association with human disease, with the exception of food-poisoning cases (Zhao et al., 2017). However, SEM's in vitro T-cell stimulating ability was found to be equal to that of SEC (Pan et al., 2007). Therefore, we suggest that this was an SEM case with SSF-associated toxin, and we believe it to be the first case to show an association between SEM and SSF.

The ages of SSF patients from previous case studies ranged from 0.2 months to 13 years (Courjon et al., 2013; Lina et al., 1997; Lo et al., 2009; Wang et al., 2004). Only one study that examined an association between enterotoxins and SSF reported two adult cases (Jarraud et al., 1999). To the best of our knowledge, no case has been reported in an elderly patient. The 74-year-old man in this case had a clinical course consistent with SSF in terms of fever and rash durations (4 days and 5 days, respectively), as well as superantigen clinical manifestations and detection (Lo et al., 2009).

SSF is usually considered a pediatric disease. However, if SSF and TSS are viewed as part of a continuum of toxin-mediated diseases, SSF may be overlooked in adults. Therefore, clinicians should consider SSF as a differential diagnosis when examining an adult patient with fever and generalized rash.

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Ethical approval

This study adhered to the principles of Good Clinical Practice, including adequate human subject protections, in accordance with the recommendations and guidance of the Samsung Medical Center's Institutional Review Board (File No. 2019-02-067).

Conflicts of interest disclosure

There are no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.05.012.

References

Chiang YC, Liao WW, Fan CM, Pai WY, Chiou CS, Tsen HY. PCR detection of Staphylococcal enterotoxins (SEs) N, O, P, Q, R, U, and survey of SE types in Staphylococcus aureus isolates from food-poisoning cases in Taiwan. Int J Food Microbiol 2008;121:66–73.

Courjon J, Hubiche T, Phan A, Tristan A, Bes M, Vandenesch F, et al. Skin findings of *Staphylococcus aureus* toxin-mediated infection in relation to toxin encoding genes. Pediatr Infect Dis J 2013;32:727–30.

Enright MC, Day NP, Davies CE, Peacock SJ, Spratt BG. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. J Clin Microbiol 2000;38:1008–15.

Grumann D, Nubel U, Broker BM. *Staphylococcus aureus* toxins—their functions and genetics. Infect Genet Evol 2014;21:583–92.

Harmsen D, Claus H, Witte W, Rothganger J, Claus H, Turnwald D, et al. Typing of methicillin-resistant *Staphylococcus aureus* in a university hospital setting by using novel software for spa repeat determination and database management. J Clin Microbiol 2003;41:5442–8.

Jarraud S, Cozon G, Vandenesch F, Bes M, Etienne J, Lina G. Involvement of enterotoxins G and I in staphylococcal toxic shock syndrome and staphylococcal scarlet fever. J Clin Microbiol 1999;37:2446–9.

Jarraud S, Mougel C, Thioulouse J, Lina G, Meugnier H, Forey F, et al. Relationships between *Staphylococcus aureus* genetic background, virulence factors, agr groups (alleles), and human disease. Infect Immun 2002;70:631–41.

Lina G, Gillet Y, Vandenesch F, Jones ME, Floret D, Etienne J. Toxin involvement in staphylococcal scalded skin syndrome. Clin Infect Dis 1997;25:1369–73.

Lo WT, Tang CS, Chen SJ, Huang CF, Tseng MH, Wang CC. Panton-Valentine leukocidin is associated with exacerbated skin manifestations and inflammatory response in children with community-associated staphylococcal scarlet fever. Clin Infect Dis 2009;49:e69–75.

Pan YQ, Ding D, Li DX, Chen SQ. Expression and bioactivity analysis of Staphylococcal enterotoxin M and N. Protein Expr Purif 2007;56:286–92.

Wang CC, Lo WT, Hsu CF, Chu ML. Enterotoxin B is the predominant toxin involved in staphylococcal scarlet fever in Taiwan. Clin Infect Dis 2004;38:1498–502.

Weisse ME. The fourth disease, 1900-2000. Lancet 2001;357:299–301.

Yamaguchi T, Nishifuji K, Sasaki M, Fudaba Y, Aepfelbacher M, Takata T, et al. Identification of the *Staphylococcus aureus* etd pathogenicity island which encodes a novel exfoliative toxin, ETD, and EDIN-B. Infect Immun 2002;70:5835–45.

Zhao Y, Zhu A, Tang J, Tang C, Chen J. Identification and measurement of staphylococcal enterotoxin M from *Staphylococcus aureus* isolate associated with staphylococcal food poisoning. Lett Appl Microbiol 2017;65:27–34.

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