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The Relationship between *Streptococcus pyogenes emm* Type and Clinical Symptoms in Balanitis Patients

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ABSTRACT

Balanitis categorized as a sexually transmitted infection is caused by the inflammation of the glans penis. Although one of the causative pathogens of balanitis is *Streptococcus pyogenes*, the relationship between bacterial markers in *Streptococcus pyogenes* and clinical symptoms has not been elucidated yet. This study analyzed the correlation between *emm* type and clinical symptoms of balanitis. Thirty-two samples of *Streptococcus pyogenes* were collected from balanitis patients in 2 medical institutes from 2009 to 2011. The *emm* type sequencing analysis was performed on the 32 strains and compared them to clinical symptoms. From balanitis patients, *emm* 11, *emm* 75, and *emm* 112 strains were the frequently isolated. Among the patients, 88% were in the age groups of 20 and 40 years. In ~66% of patients, the symptoms appeared between 4 and 14 days. With regard to the relationship between *emm* type and swelling of the penis, *emm*11 strain showed higher penile swelling compared to the other *emm* type strains (p = 0.0354). All *emm* 58 strains caused itching. Only 3 (*emm* 58, *emm* 73, and *emm* 75) *emm* type strains caused purulent discharge from the penis. This suggests that specific *emm* types *Streptococcus pyogenes* are associated with balanitis.

KEYWORDS: balanitis, *emm* type, *Streptococcus pyogenes*

INTRODUCTION

Sexually transmitted infection is illness that has a significant probability of transmission between humans by means of human sexual behavior, including vaginal intercourse, oral sex, and anal sex (Mandell et al., 2010). Balanitis is categorized as a sexually transmitted infection, and it is defined as an inflammation of the glans penis, which often involves the prepuce (Birley et al., 1993; Edwards, 1996). Inflammation can be caused by infection with a wide variety of pathogens, including bacteria, viruses, or fungi (Mandell et al., 2010). It is a common condition that affects ~10% of male genitourinary clinic attendees; it can be a recurrent or persistent condition (Wakatsuki, 2005).

Streptococcus pyogenes (*S. pyogenes*) causes numerous infectious diseases such as pharyngitis, tonsillitis, nephritis, scarlet fever, necrotizing fasciitis, and streptococcal toxic shock syndrome (STSS) (Cunningham, 2000). *S. pyogenes* is also the causative agent of balanitis (Mandell et al., 2010). An investigator reported pyoderma of the penis followed fellatio, with *S. pyogenes* being isolated from the coronal sulcus (Drusin et al., 1975). There have been several short reports, including case reports, confirming the Streptococcal origin of balanitis (Deliyanni et al., 1989; Guerrero-vazquez et al., 1990; Kyriazi et al., 1991; Orden et al., 1995, 1996., 2000; Leverkus et al. 2002; Sakuma et al., 2005; Wakatsuki 2005; Nicolas et al., 2006). However, the bacterial pathophysiology and epidemiology of streptococcal balanitis has been unclear. Although the authors have reported 4 cases of streptococcus balanitis in the past, they were unable to elucidate the etiology of streptococcal balanitis owing to the limited number of cases (Minami et al., 2010).

M proteins are fibrillar coiled-coil proteins that are localized on the bacterial surface in *S. pyogenes* (Perez-Casal et al. 1993). M proteins are comprised of up to 4 distinct repeat regions and are anchored to the cell surface by a highly conserved C-terminal domain (Perez-Casal et al. 1993). The N-termini form highly variable extracellular fibrils. M proteins are associated with immune evasion mechanisms (Perez-Casal et al., 1993).

The classification of *S. pyogenes* was widely performed by comparison to the nucleotide sequence analysis of M protein—the *emm* type sequencing analysis. Similar to the N-terminus variability of the M proteins, the genes encoding M proteins (*emm* genes) also exhibit genetic variability (Beall et al., 1996). The nucleotide sequence of the variable 5' end of the *emm* gene serves as the template for *emm* sequence typing. (Beall et al., 1996).

Previous reports have showed that specific *emm* type *S. pyogenes* were frequently observed to cause severe invasive diseases, thereby suggesting that *emm* type could be a predictive marker of certain severe types of streptococcal diseases (Rogers et al., 2007; Steer et al., 2009; Lin et al., 2011). However, the distribution of *emm* type patterns in *S. pyogenes* from balanitis patients has not yet been reported. Hence, this study has attempted to clarify the relationship between *emm* type and clinical symptoms in streptococcal balanitis.

Objectives of the study

Our general objective is to assess the relationship between *S. pyogenes emm* type and clinical symptoms in balanitis patients. Furthermore, our specific objectives are to correlate the different *S. pyogenes* strains with the severity of balanitis, with other clinical markers, and with patients' demographic data.

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MATERIALS AND METHODS

Collection of clinical data

A prospective study was conducted in Nagoya City University Hospital, and Tawada Urological Clinic in Nagoya City, that assessed the clinical features of streptococcal balanitis that occurred between 2009 and 2011. Details of age, duration of infection, and the occurrence of clinical symptoms such as penile swelling, penile itching, and pus discharge, were collected from the medical records of both institutions. Streptococcal balanitis was defined by *S. pyogenes* isolates from the penis accompanied by penile reddening, which was diagnosed by urologists. The ethics committee at Nagoya City University approved of the experimental design.

Ethical statement and patient's consent

Written/verbal consent of patients was taken, after private discussion with each one of the patients, explaining the study objectives and the need for samples and clinical data collection. Patients' confidentiality was maintained throughout the study period.

Samples

Thirty-two *S. pyogenes* clinical isolates were obtained from male patients with balanitis. Bacteria were identified on the basis of the growth of β-hemolytic colonies on sheep blood agar after incubation at 37°C in 5% CO_2 for 18–24 h. A confirmatory test for *S. pyogenes* was carried out with the Streptgram kit (Wako Chemical Inc., Tokyo, Japan). The bacterial 16S ribosomal sequencing analysis was also performed for genetic confirmation (Minami et al., 2010).

emm type sequencing analysis

Bacteria were characterized by *emm* type sequencing, as described previously (Beall et al., 1996). These nucleotide sequences data of *emm* type were further compared according to the available information from the Centers for Disease Control and Prevention surveillance studies (Availableat: http://www.cdc.gov/ncidod/biotech/strep/strepindex.htm).

Statistical analysis

Chi square analysis and F-test were used to analyze the data, and $p < 0.05$ (95% confidence) was considered statistically significant. Analysis was performed using Statview computer software Version 4 under Mac OS 9.

RESULTS

The distribution of *emm* type in *S. pyogenes* from balanitis patients

Figure 1 shows the distribution of *emm* type patterns in *S. pyogenes* in this study. There were 5 *emm* 11 type strains, which were most frequently isolated. The second largest number of strains isolated was *emm* 75 and *emm* 112 (n = 4). The third largest number of strains included the *emm* 73, *emm* 77, *emm* 81, and *emm* 89 strains (n = 3). These 3 strains comprised ~70% of the total isolates. There was no significant number of specific *emm* type strains in this study.

Correlation between *emm* type and patients' age

Table 1 shows the relationship between *emm* type and patient's age. The number of patients aged 20 years and 40 years was 14, and 12, respectively; these 2 age groups constituted ~88% of the total number of patients. However, the numbers of 30- and 50-year-old patients were fewer than both the 20- (n = 3) and 40-year-old patients (n = 2). No 60-year-old patients were found in this study. It was found that there was no significant relationship between *emm* type and age in this study.

Correlation between *emm* type and duration of symptoms
Table 2 shows the relationship between *emm* type and duration of the symptoms. In ~66% of patients, the symptoms appeared within 4–14 days. The frequency of symptoms before 3 days, and after 15 days, was negligible. There was no significant relationship between *emm* type and duration of the symptoms in this study.

Correlation between *emm* type and swelling of penis

Figure 2 shows the relationship between *emm* type and penile swelling. While *emm* 11 strains caused more swelling of the penis than the other *emm* type strains ($p = 0.0354$), four (*emm* 50, *emm* 73, *emm* 77, and *emm* 89) *emm* type strains did not cause penile swelling.

Correlation between *emm* type and penile itching

Figure 3 shows the relationship between *emm* type and penile itching. Both all *emm* 50 and *emm* 58 strains caused penile itching, while none of the *emm* 112 strains did. However, there was no significant relationship between these *emm* types and penile itching in this study.

Correlation between *emm* type and secretion of pus from the penis

Out of 32 patients, 3 patients had pus secretion from the penis. The *emm* type patterns of *S. pyogenes* strains isolated from these patients were *emm* 58, *emm* 73, and *emm* 75, respectively.

DISCUSSION

To the authors' best knowledge, this is the first report of the elucidation of the relationship between *emm* type and clinical symptoms in balanitis caused by *S. pyogenes*. No previous reports have investigated bacterial factors including *emm* type, in patients with streptococcal balanitis. From the study's results, it can be seen that minor *emm* type strains cause balanitis; these are different from STSS-caused *S. pyogenes* which predominantly include strains *emm* 1, and *emm* 3 (Cunningham, 2000; Steer et al., 2009; Lin et al., 2011). This study has not assessed if those *S. pyogenes* caused STSS following balanitis. The *emm* type strains causing balanitis were also different from those that caused pharyngitis. The majority of *emm* type strains causing pharyngitis in Japan are currently *emm* 12, *emm 4*, and *emm 1* (Wajima et al., 2008).

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The study's results suggest that a new category of *emm* type exist among the balanitis-causing strains, and hence, authors were interested in investigating the colonization patterns of these *emm* type strains.

The relationship between *emm* type and patients' age implies that there are a higher number of patients in the 20- and 40-year-old groups. From this result, one speculates that young and middle-aged male patients have higher sexual activity and a higher possibility of contact with commercial sexual workers. In fact, contact with sexual workers is one of the major risk factors in sexual transmitted diseases (Wakatsuki, 2005).

Previous reports have shown that streptococcal balanitis occurs mainly in the age group of 30 years (Wakatsuki, 2005); however, the results at hand do not reiterate this finding. As the study did not find the reason the number of 30 years male patients was decreasing, further accumulation of patient's data may resolve this question.

The relationship between *emm* type and duration of the symptoms also suggest that the symptoms of balanitis occur within 1–2 weeks, and not within a few days. A previous report showed that streptococcal balanitis occurred within a few days after sexual contact (Wakatsuki. 2005). There could be differences in onset time between pharyngitis and balanitis. The duration of pharyngitis is a few days (Cunningham, 2000), and this time interval coincides with that in a previously reported balanitis report (Wakatsuki, 2005).

Although these differences have not been explained clearly, the severity of balanitis, and the virulence of *S. pyogenes* isolates raise important questions, which need to be investigated.

When patients develop symptoms such as itching and pus secretion, most of them may consult an outpatient clinic because of the severity of the symptoms. After consultation, most patients in Japan may immediately receive antibiotics for infections caused by *Neisseria* or *Chlamydia* before the causative bacterium is identified (Wakatsuki, 2005). Antibiotics such as fluoroquinolone are also effective against *S. pyogenes*; this could possibly be one of the reasons that patients with streptococcal balanitis do not spread the infection, and could also explain the lack of attention paid to balanitis caused by *S. pyogenes*.

In the present study, the relationship between *emm* type and penile swelling shows that a specific *emm* type (*emm* 11) caused significant penile swelling more frequently than other strains. The authors were unaware that *emm* 11 *S. pyogenes* possessed specific high virulent factors, and hence, are currently investigating the novel putative virulent factors. The relationship between *emm* type and penile itching shows that *emm* 58 *S. pyogenes* had high virulence, and *emm* 112 had low virulence. Current results also show that ~10 % of balanitis patients had pus discharge from the penis. Specific *emm* type (*emm* 58, *emm* 73, and *emm* 75) strains were observed in this study. An earlier report showed that symptoms of pus discharge and penile itching were predominant in balanitis (Wakatsuki, 2005).

Although similar results were observed on penile itching, they were not the same for pus discharge. These differences might explain the severity of balanitis between the earlier reports and the current.

In conclusion, the study's results suggest that a specific *emm* types *S. pyogenes* are associated with balanitis. The *emm* type sequencing analysis may be a useful marker for the prediction of progressive disease activity.

Recommendations for further Studies

Further accumulating patient's data is necessarily for confirmation of the colonization patterns of specific *emm* type *S. pyogenes* in balanitis patients. The relationship between severity of balanitis and the virulence of *S. pyogenes* isolates also need to be clarified.

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COMPETING INTERESTS

The authors declare no competing interests.

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TABLES AND FIGURES

Table 1. The relationship between *emm* type and patient's age.

	emm type										
age	11	28	50	58	73	75	77	81	87	89	112
20-29	3	0	1	0	1	1	2	2	1	2	1
30-39	0	0	0	1	1	0	1	0	0	0	0
40-49	2	2	0	1	1	1	0	0	1	1	3
50-59	0	0	0	0	0	2	0	0	0	0	0
60-69	0	0	0	0	0	0	0	0	0	0	0
70-79	0	0	0	0	0	0	0	1	0	0	0

Table 2. The relationship between *emm* type and duration of symptoms

	emm type										
age	11	28	50	58	73	75	77	81	87	89	112
1-3	1	1	0	2	0	0	0	1	1	0	0
4-7	1	1	0	0	1	2	0	1	0	1	1
8-14	3	0	1	0	2	1	2	0	1	2	3
15-28	0	0	0	0	0	1	1	1	0	0	0

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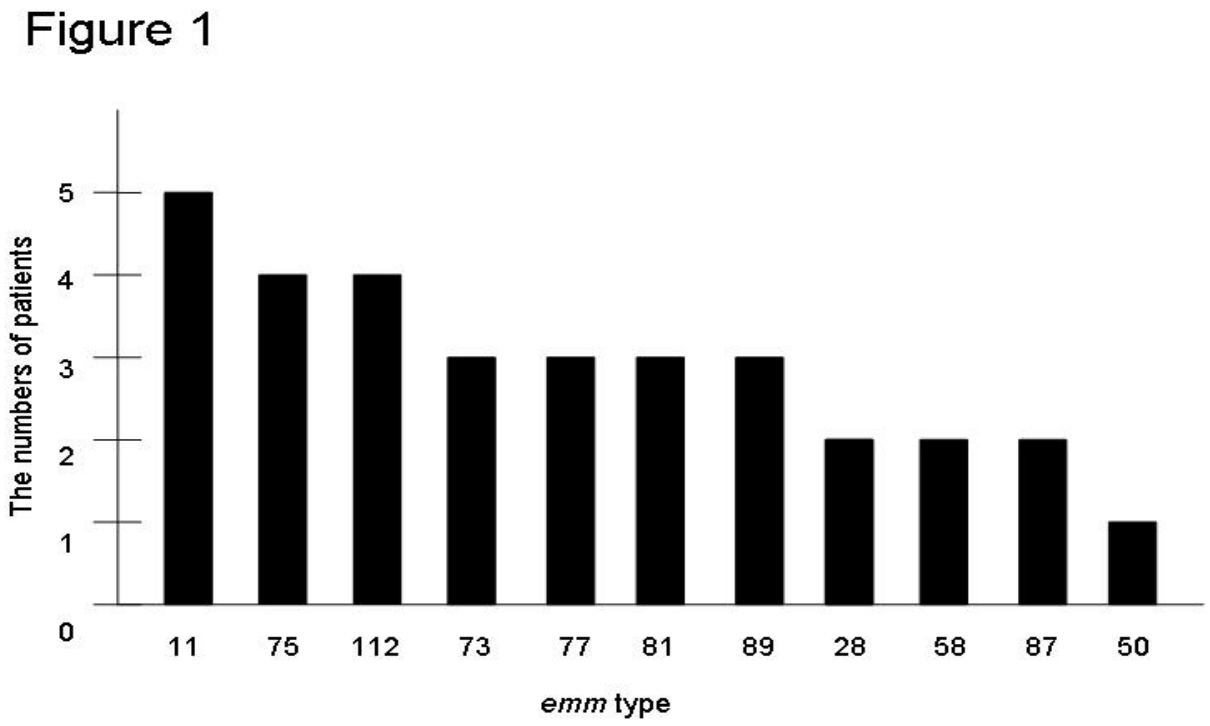

Fig 1. The relationship between *emm* type and the numbers of streptococcal isolates from balanitis patients.

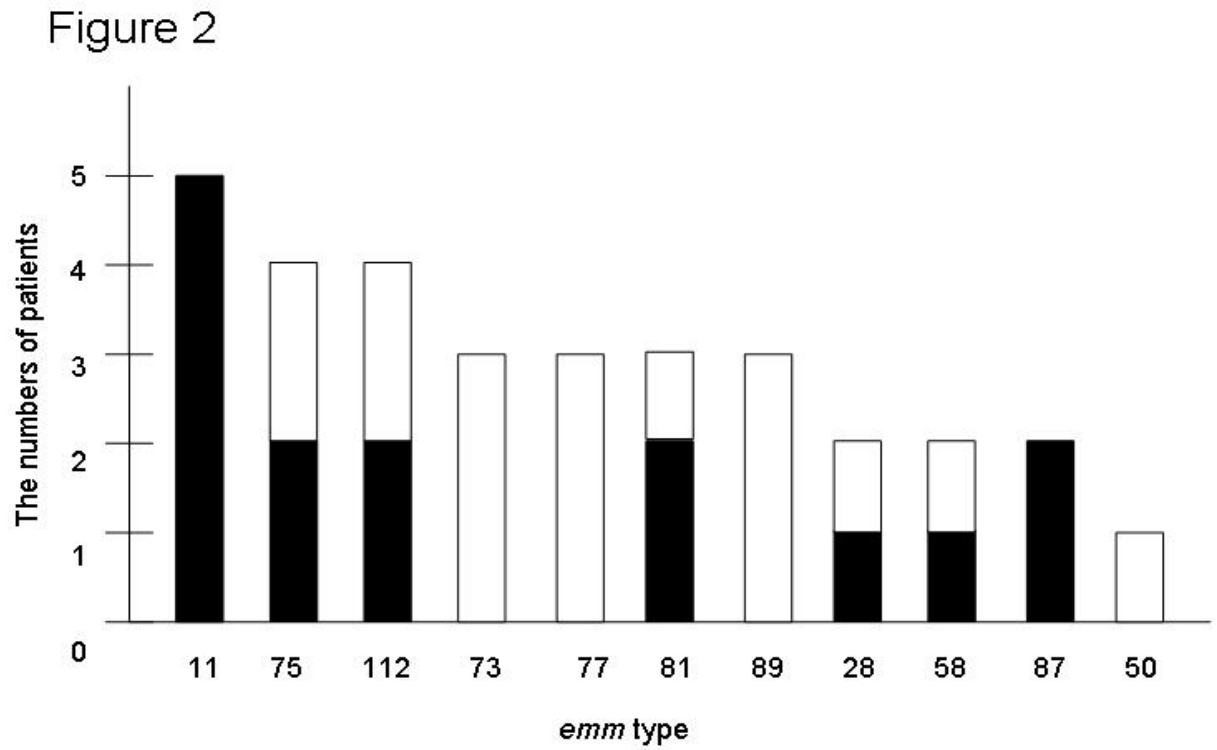

Fig 2. The relationship between *emm* type and penile swelling.

The black and white boxes represent positive and negative for penile swelling in balanitis patients, respectively.

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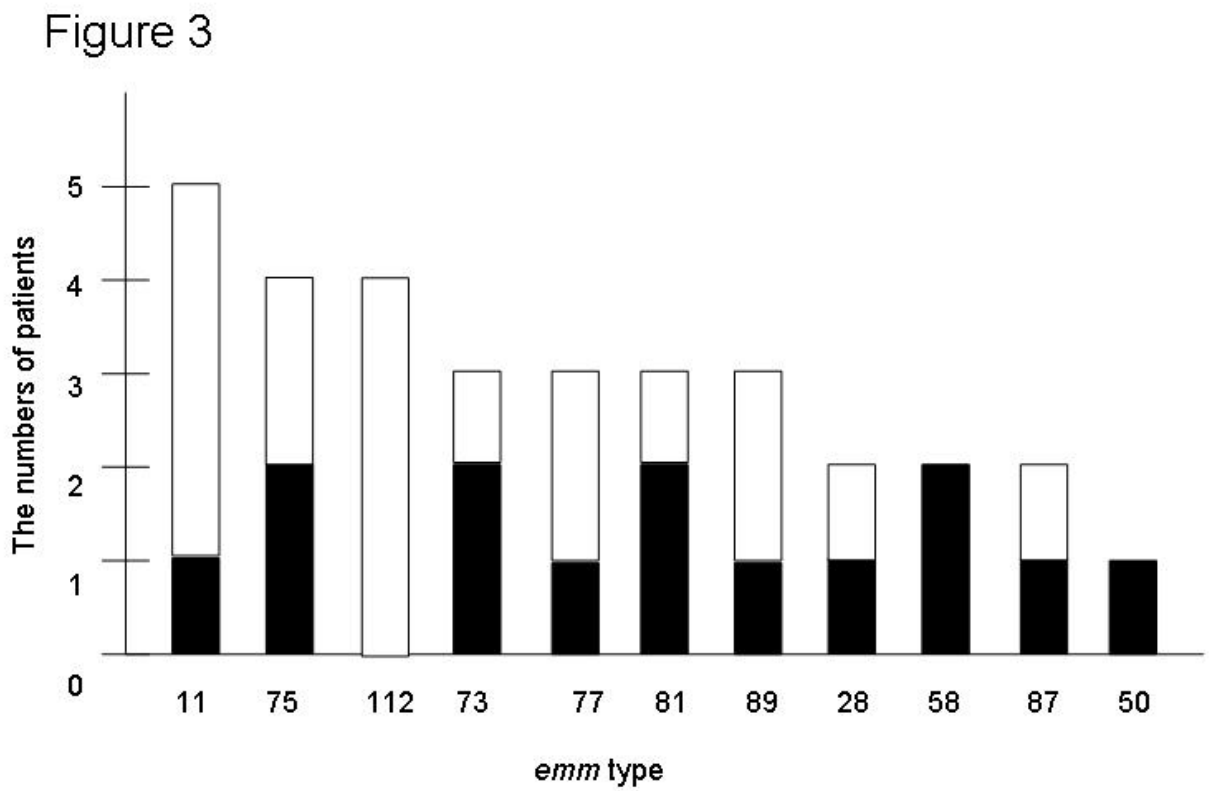

Fig 3. The relationship between *emm* type and penile itching.

The black and white boxes represent positive and negative for penile itching in balanitis patients, respectively.

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