Familial Transmission of a Serious Disease–Producing Group A Streptococcus Clone: Case Reports and Review

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Invasive group A streptococcus (GAS) infections are emerging diseases; however, person-to-person transmission of invasive GAS producing life-threatening infection has been observed rarely. We report a small intrafamilial cluster of life-threatening GAS infections. A previously healthy 47-year-old father developed necrotizing fasciitis of the neck. Two days later, his 16-year-old daughter developed streptococcal angina, pneumonia, and pleural empyema. Both patients had signs of streptococcal toxic shock syndrome. Pulsed field gel electrophoresis revealed that the M6 strains of GAS isolated from the father and daughter had identical patterns. Cases of person-to-person transmission of invasive GAS infection reported in the literature are also reviewed.

There are three important categories of group A streptococcus (GAS) infections: localized infections such as pharyngitis, invasive (superficial) infections such as erysipelas, and acute life-threatening diseases such as necrotizing fasciitis, streptococcal toxic shock syndrome (TSS), and streptococcal myositis [1, 2]. Furthermore, GAS infections may be followed by non-suppurative complications such as rheumatic fever and glomerulonephritis.

In recent years, the incidence of invasive GAS infections has apparently increased. The precise reasons are unknown. Several explanations such as the emergence of new clones have been proposed [3]. In 1994, the Centers for Disease Control and Prevention estimated that 10,000–15,000 cases of invasive GAS infections occur annually in the United States; 5%–10% (500–1,500) of these cases are necrotizing fasciitis (overall mortality rate, ~28%) [4].

It is well known that GAS causing pharyngitis can easily be spread from person to person via droplets. In rare instances, person-to-person transmission of invasive GAS infection has been described [5–13]. Only a few cases of transmission from a mother to an infant [7], between members of a family [8–10], during cardiopulmonary resuscitation [11], and between residents of nursing homes [12, 13] have been reported. We describe intrafamilial transmission of GAS producing life-threatening infections in a father and daughter.

Case Reports

Case 1

A previously healthy 47-year-old man developed fever (temperature, 38°C), cough, sore throat, and general myalgias. Within 3 days, his temperature was 40°C, and he had chills and severe pain in the left side of his neck, where he noted a dark lesion surrounded by erythema. In the following hours, he had nausea, watery diarrhea, and dizziness and vomited. He was admitted to the local hospital.

At the time of admission, his temperature was 39.8°C, and he had hypotension (blood pressure, 90/60 mm Hg), tachycardia (heart rate, 110), and tachypnea (respiratory rate, 30). Renal failure (serum creatinine level, 260 μmol/L) and a scarlatina-like erythema on the limbs were noted. Bilateral enlargement of the submandibular lymph nodes was observed, as were two dark blue indurated lesions (4×4 cm) on the left side of the neck; the lesions had irregular borders surrounded by a large, sharply delimited erythema. Laryngeal examination revealed swelling of the recessus piriformis on the right side and a rapidly progressive swelling of the laryngotracheal mucosa.

Laboratory studies showed the following: leukocyte count, normal (60% band forms with toxic granulations and vacuoles); C-reactive protein level, 350 mg/L (normal, 0–10 mg/L); serum albumin level, 29.5 g/L (normal, 35–50 g/L), and creatine phosphokinase level, 1,433 U/L (normal, 50–200 U/L). Six blood cultures yielded no growth. Intravenous fluids (3,000 mL) and catecholamines (dopamine, 200 μg/min; dobutamine, 200 μg/min) were administered, and treatment with flucloxacillin (2 g t.i.d.) and clindamycin (600 mg t.i.d.) was started. The patient's condition remained critical, and he was transferred to the university hospital.

CT of the neck showed diffuse thickening of soft tissues (cutis, subcutis, and platysma) in the entire neck area; the thickening was more prominent on the left side. Tracheotomy and bilateral neck incision with extensive debridement and drainage of the anterior neck were performed. Debridement was repeated 2 days later because of progressive subcutaneous necrosis. Cultures of tissue fluid and tissue specimens from the neck yielded GAS.

Flucloxacillin therapy was replaced by intravenous penicillin G therapy (2 million U t.i.d.; dose adjusted because of renal failure), and clindamycin treatment was continued. He was treated with high doses of penicillin for 4 weeks and with clindamycin for a total of 10 days (this therapy was interrupted following the onset of diarrhea) [14]. The patient's condition improved rapidly; he was discharged from the hospital in good health without medication 1 month later.

Case 2

The daughter of the patient in case 1, a 16-year-old healthy student, had upper respiratory tract symptoms and watery diarrhea 2 days after her father became ill. She was admitted to the local hospital because of general malaise and bilateral chest pain.

At the time of admission, her temperature was 37.8°C, and she had hypotension (blood pressure, 85/45 mm Hg), tachycardia (heart rate, 130), and tachypnea (respiratory rate, 25). Acute pharyngitis and tonsillitis were noted. Chest roentgenography showed bilateral infiltrates with pleural effusions (which were larger on the right side). Laboratory studies revealed the following: leukocyte count, normal (67% band forms with toxic granulations and vacuoles); C-reactive protein level, 370 mg/L; and serum albumin level, 29.4 g/L.

Cultures of specimens from the pharynx, nasopharyngeal secretions, and right pleural effusion yielded GAS. The larger right pleural effusion was drained, and treatment with intravenous penicillin G (4 million U q4h) and intravenous clindamycin (900 mg t.i.d.) was initiated. She was transferred to the university hospital because of persistence of a toxic state in spite of adequate medical therapy.

At the time of admission, a CT scan of the chest showed bilateral infiltrates compatible with acute respiratory distress syndrome with consolidation of the right lower lobe, bilateral pleural effusions with contrast enhancement, and mediastinitis. Extensive thoracic surgery was performed. Her clinical course was uneventful after surgery. She was treated with high doses of penicillin and with clindamycin for a total of 25 days.

Microbiological Survey

Throat swab specimens were not obtained from the remaining family members. They were all given penicillin prophylaxis. Cultures of throat swab specimens from 27 health care workers did not yield GAS.

Microbiological Analysis

Four isolates of GAS were available for further study, one from the father and three from the daughter. Standard laboratory identification techniques revealed that these isolates had identical characteristics. M protein typing of the isolate from the father and one isolate from the daughter was performed; it showed that M protein type 6 was present in both strains. The same isolates from both patients were also compared by means of pulsed field gel electrophoresis of SmaI–digested genomic DNA as previously described [10]. The DNA fingerprints of the isolates from both patients were compared with those of five epidemiologically unrelated M6 isolates of Streptococcus that were recovered from patients with severe infections who were seen in the United States (figure 1).

Discussion

The interest in necrotizing fasciitis as a serious manifestation of invasive GAS infection increased in 1989 following the report of 20 cases of streptococcal TSS [15]; 11 of these patients also had necrotizing fasciitis. More recently, cases of acute life-threatening GAS infections associated with high mortality rates have been reported, predominantly from North America and Europe [1, 2, 5]. In these studies, most patients were previously healthy. However, in a population-based study from Canada [6], patients with underlying conditions (e.g., cancer, HIV infection, and diabetes) were at higher risk for invasive GAS infections. Most of the cases were not epidemiologically related.

The epidemiology of invasive GAS infections is not well understood [5, 6, 16]. A retrospective review of cases of infection due to invasive GAS isolated from blood or other sterile sites was done in 10 hospitals in Pima County, Arizona, during 1985–1990 [16]. The annual incidence was 4.3 cases per 100,000 residents, and 6.5% of all cases of invasive GAS infections were necrotizing fasciitis. In a recent study [6], an annual incidence of 1.5 cases of invasive GAS infections per 100,000 population was observed, with fasciitis and TSS occurring in 6% and 13% of patients, respectively. These investigators estimated that the incidence among household members of patients was 2.9 cases per 1,000 population, almost 200 times the incidence among the general population. However, no household contact had TSS in this study.

We describe intrafamilial transmission of acute life-threatening GAS infection in a father and daughter. The father had necrotizing fasciitis and typical streptococcal TSS according to the previously reported case definitions [1]. His daughter presented with streptococcal TSS and developed necrotizing intrathoracic infection with acute respiratory distress syndrome. Molecular analysis showed that the GAS isolates from the father and daughter were identical. We are aware of only a few reports where clusters of acute life-threatening GAS infections in two patients have been documented [9, 10, 12]. In one
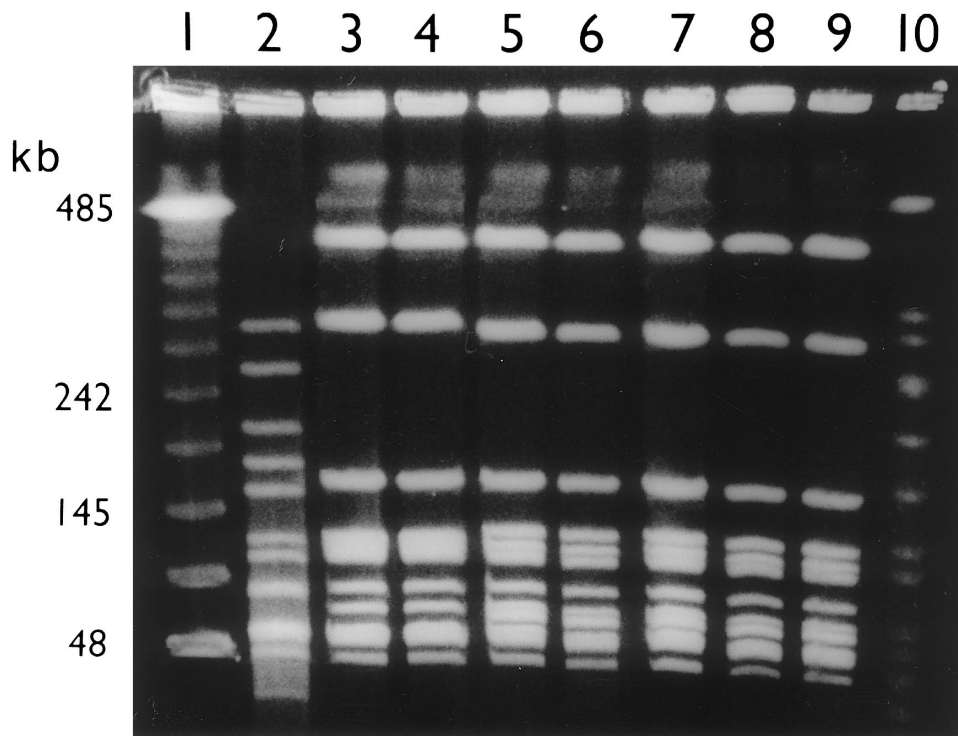
Figure 1. Pulsed field gel electrophoresis patterns of *Sma*I–digested chromosomal DNA from M6 strains of group A *Streptococcus.* Lane 1, molecular size standard for bacteriophage λ ladder; lanes 2 and 10, organism controls (group A *Streptococcus* serotype M3 and *Staphylococcus aureus,* respectively); lanes 3 and 4, M6 isolates from cases 1 and 2, respectively; lanes 5–9, M6 isolates from patients with severe streptococcal infections who were seen in the United States. kb = kilobases.

instance, transmission of streptococcal TSS from a daughter to a mother (both died) was observed [9]. Another report described transmission from a patient with streptococcal TSS to a household member who developed both streptococcal TSS and necrotizing fasciitis [10]. In a nursing home cluster, both the index patient and a secondary patient had necrotizing fasciitis [12].

Transmission of invasive GAS infection remains to be elucidated. The rare reports of clustering of life-threatening GAS infections suggest several explanations. First, serious GAS infection is by itself a rare event. Second, since soft-tissue infections are the most frequent primary manifestations of invasive GAS infection, transmission under these circumstances may be less efficient.

While strains causing soft-tissue infections may not be easily transmitted in communities with acceptable levels of hygiene, patient-to-patient transmission or transmission via health care personnel or instruments in special settings (such as nursing homes or hospitals) is a possibility. Whereas GAS causing pharyngitis is readily spread by direct person-to-person contact (often via droplets of saliva or nasal secretions), person-to-person transmission of acute life-threatening GAS infections is poorly understood. However, an investigation of nosocomial clustering [17] has pointed to asymptomatic or symptomatic pharyngeal carriage of GAS by health care personnel as a possible way of transmission.

Schwartz et al. [5] described clusters of invasive GAS infections between 1988 and 1992 in family members, hospital personnel, and nursing home residents. Although 12 family household clusters were described, no case of necrotizing fasciitis occurred. Recent reports demonstrated familial transmission of serious disease–producing clones [9, 10]. In these reports, strains were M protein types 1 and 3, respectively. M protein type 6 was found in our cases. Recently, most strains recovered from patients with serious disease have been M protein types 1, 3, 12, or 28 [1].

In summary, to our knowledge, we report the first cases of streptococcal TSS caused by M6 strains of GAS. Moreover, pulsed field gel electrophoresis showed that the isolates were identical, thus demonstrating familial transmission. The use of molecular analysis of strains will be essential in future studies assessing the proportion of cases of invasive GAS infections with definitive epidemiological links.

Although largely anecdotal, our findings together with the previously reported observations about transmission of life-threatening GAS infections [5, 6, 9, 10, 12, 16] raise the question of preventive antibiotic treatment of contacts of patients. It is unlikely that controlled clinical trials with sufficient power to resolve the value of preventive treatment will be performed.

On the basis of our observations and those of published reports of transmission of invasive GAS infections, we prefer to administer preventive treatment (particularly to those in contact with secretions), similar to that for close contacts of patients with streptococcal pharyngitis, or to culture specimens from close contacts (inside and outside the hospital) and treat those for whom cultures are positive. It is the primary physician caring for these patients who must judge

the risks on the basis of exposure and manage the considerable concerns of those in close contact with the patient.

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