Familial Transmission of Necrotizing Fasciitis Caused by Group A *Streptococcus pyogenes*

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Abstract

"Necrotizing fasciitis is an invasive, life-threatening disease, frequently caused by *Streptococcus pyogenes* (Group A *Streptococcus*: GAS). Cases are already documented but the worldwide incidence has increased in recent years. Here we propose two unusual cases of potential intrafamilial transmission of necrotizing fasciitis and describe the clinical course in each patient."

A 66-year-old man was admitted to our hospital with a necrotizing soft tissue infection of the lower leg and five days later his partner was hospitalized with a necrotizing fasciitis of the neck and chest. After multiple surgical interventions and extensive intensive medical care, the male patient was discharged but his partner developed a multiple organ failure and died 27 h after hospitalization.

Isolates of GAS from both patients were analyzed at the reference laboratory applying M protein (emm) gene typing and multiplex PCR screening for superantigen genes. The results of the microbiological examination support the hypothesis of intrafamilial transmission of a *S. pyogenes* emm89.0 strain. This clinical presentation shows a case of rapid onset necrotizing fasciitis with lethal outcome despite aggressive multimodal treatment. Both patients lived in the same house but were separately admitted a few days apart. Person-to-person transmission of necrotizing fasciitis caused by *Streptococcus pyogenes* is rare, but should be considered.

Keywords: Necrotizing fasciitis; *Streptococcus pyogenes*; Familial transmission

Introduction

Necrotizing fasciitis is a fulminating infection of the soft tissues caused by aerobic and anaerobic organisms. The infection spreads through the fascial planes and often results in extensive tissue necrosis [1,2]. Recent evidence shows increasing numbers of invasive infections caused by *Streptococcus pyogenes* [3]. From 2007 to 2017, the overall mortality rate increased with the rising numbers of infections [3,4]. In the last four decades, several European countries and the United States reported rising numbers of severe outbreaks caused by *Streptococcus pyogenes* [5]. To investigate the epidemiology of this disease, the Strep-EURO program was founded in 2002 [5]. Seasonal patterns and similar risk factors were found in all countries. In the majority of cases, minor skin injury was the trigger for the invasive *Streptococcus pyogenes* infection and the rising incidence was confirmed [6]. Clinically, necrotizing fasciitis varies in severity but early diagnosis and radical intervention are essential to avoid a fatal outcome. The most common classification is defined by the microbial origin of infection (Table 1) [7].

An infection with Group A streptococcus can lead to localized infections such as pharyngitis, superficial tissue infections or progressive infections such as necrotizing fasciitis. It is well known, that a familial or nosocomial transmission of this bacterium is possible. There are multiple cases of GAS infections in the literature that describe the spread of pharyngitis from person to person [8,9]. In addition, family transmission of GAS-induced orbital cellulitis [10] and cases of familial or nosocomial GAS transmission of necrotizing fasciitis with toxic shock syndrome are documented [11,12]. This is the first report of cohabitating patients that developed similar Type II necrotizing soft tissue infections caused by *Streptococcus pyogenes*, with a 50% fatal outcome.
Patients and Methods

Two patients with a short history of rapid onset soft tissue swelling and pain presented to our medical Centre. The patients were aged 66 and 62 years. Clinical diagnoses of necrotizing fasciitis became apparent and rapid surgical intervention was needed. Subsequent investigations revealed that the two cases of invasive GAS infections occurred within one household and the isolates were sent to the German national reference Centre on streptococcal diseases. The remaining family members and health care workers were not screened.

Prior to the antibiotic treatment, paired blood samples were taken and the Time to Positivity (TTP) in the aerobic and anaerobic culture flasks was at 9.8 and 10 h in case 1 and at 6.3 and 7 h in case 2. Despite antibiotic therapy, the tissue cultures showed active growth in most samples of both cases, after one day of enrichment.

**Case 1**

A 66-year-old man with a history of diabetes, prior abscess on the right thigh due to *Staphylococcus aureus* (MSSA), atrial fibrillation, prostate carcinoma and chronic venous insufficiency was admitted with sudden onset of painful soft tissue swelling of the lower leg. The temperature on admission was 39.3°C and the White Blood Cell (WBC) count was 15.4/nl. Other relevant parameters included a blood pressure of 80/65 mmHg, heart rate of 113 and oxygen saturation of 95%. The C-Reactive Protein (CRP) was 23.7 mg/dl.

The laboratory values are shown in Table 3.

Blood samples were taken and antibiotic therapy was commenced one hour after hospital admission using 4.5 g piperacillin/tazobactam every six hours. Close monitoring revealed a worsening “cellulitis” and the patient proceeded to surgery ten hours after admission. Clinical examination revealed a new necrotic lesion on the left lower leg with blistering and a lymphangitis with cellulitis (Figure 1a and b).

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A subfascial debridement of all suspicious tissue was performed and biopsies were taken for microbiological and patho-physiological examination (Figure 1c, 1d). Intraoperatively, the WBC count was...
14.9/nl, SCr of 2.67 mg/dL, Hb 12.2 g/dl, Sodium 136 mmol/l, CRP 27.3 mg/dl and PCT 63.39 ng/ml.

Postoperatively the patient required high doses of pressors to maintain his blood pressure and high-volume fluid support. A postoperative Transthoracic Echocardiography (TTE) showed early right heart failure and possible cardiomyopathy. His acidosis was buffered with TRIS. After 24 h his laboratory values were a WBC count of 25.2/nl, SCr of 2.18 mg/dL, Hb 7.9 g/dl, Sodium 142 mmol/l, PCT 62.59 ng/ml, IL-6 736.1 pg/ml and Glu 148 mg/dl. His overall clinical condition remained stable. Another laboratory blood sample control on the sixth day of the treatment showed a WBC count of 43/nl, SCr of 1.17 mg/dL, Hb 8.5 g/dl, sodium 145 mmol/l, PCT 3.90 ng/ml, and CRP 4.2 mg/dl.

On the seventeenth day, further debridement was performed and Matriderm® was applied to the wound and held in place through vacuum assisted closure. On the fifty-fifth day, soft tissue cover was applied with a free latissimus dorsi-flap, a proximal pedicled lateral gastrocnemius flap and a split skin graft. The patient required further revisions operations until healing was completed (Figure 1e).

The first blood cultures, taken on day 1 were positive for Streptococcus pyogenes. The same was observed from cultures of the lower leg. However, tissue cultures of the thigh were found to be negative for S. pyogenes. On day 2, the patient was commenced on vancomycin 1 g every 12 h; penicillin G 10 Mio IE 4 times per day and piperacillin/tazobactam 4.5 g every 6 h. The intraoperative biopsies from the wound grew Klebsiella oxytoca, Candida albicans, Staphylococcus epidermidis, Staphylococcus hemolyticus, Pseudomonas aeruginosa, Vancomycinresistant Enterococcus faecium, Enterobacter cloacae, Citrobacter koseri and E coli. A change in the antibiotic therapy was performed. This included meropenem 1 g every 8 h, fluconazole 400 mg every 12 hours, linezolid 600 mg every 12 h and levofloxacin 500 mg every 24 h. The pathological results of the biopsies from the first surgical intervention were available on the eighth day and showed a pronounced acute purulent phlegmonous fasciitis of the leg with inflammation of the included subcutaneous fat and multiple areas of calcified fat necrosis. The patient was discharged on day 111.

**Case 2**

Five days after hospitalization of the patient in case 1 his partner was admitted to the hospital. A 62-year-old woman had a history of alcohol abuse, atrial fibrillation, herpes zoster and presented with a suspected acute coronary syndrome. Prehospital aspirin and amiodarone were administered. She complained of shoulder and neck pain. Peripheral pulses were not palpable. There was necrosis of the index finger of the left hand and a history of crush injury. She presented with a temperature of 36.2°C, a WBC count of 15.3/nl, SCr of 2.6 mg/dL, Hb 14.6 g/dl, D-Dimer 3.73 mg/l, Sodium 120 mmol/l, Glu 79 mg/dl, PCT 5.33 ng/ml, IL-6 14937.0 pg/ml, CRP 40.7 mg/dl and blood pressure of 80/60 mmHg, heart rate of 144 and oxygen saturation of 80%. In order to provide a better overview of the laboratory values, these are shown in Table 4.

Blood cultures were obtained and antibiotic treatment commenced one hour after hospital admission with 4.5 g piperacillin/tazobactam every six hours. Follow up laboratory examination of blood samples after ten hours showed an increased IL-6 titer of 30708 pg/ml.

Twelve hours after admission a computerized tomography scan was performed as part of an investigation of severe cellulitis of the left arm and the anterior chest wall. A peripheral pulmonary embolism in the right inferior lobe was noted and diffuse infiltration of the subcutaneous fatty tissue of the left chest wall. Further images suggested an additional pancreatitis. The patient was started on vancomycin 1 g every eight hours, clindamycin 600 mg every eight hours, penicillin G 10 IE six times a day and piperacillin/tazobactam 4.5 g every six hours. She required vasoactive therapy...
with norepinephrine and vasopressin and remained hypotensive and tachycardic despite adequate fluid resuscitation. Eleven hours after hospitalization she was intubated due to respiratory failure. A Transthoracic Echocardiography (TTE) and a Transesophageal Echocardiography (TEE) were normal. Fourteen hours after admission, the patient rapidly developed progressive necrotic blisters on the left breast. She was taken directly to the operating room. The clinical signs included necrotic lesions on the back, the left index finger, left breast and chest wall (Figures 2a-2d). A subfascial debridement of all suspicious tissue was performed. Findings included map-like blue-red lesions with epidermolysis and edematous subcutaneous tissue with milky discolored muscles. Intraoperative laboratory blood values after 12 h were as follows a WBC count of 14.5/nl, SCr of 2.04 mg/dL, Hb 9.8 g/dl, Sodium 136 mmol/l and CRP 16.5 mg/dl. After blood transfusion and fresh frozen plasma, the following laboratory values were obtained: A WBC count of 18.5/nl, SCr of 1.99 mg/dL, Hb 10.5 g/dl, Sodium 136 mmol/l, PCT 6.10 ng/ml, IL-6 18562.0 pg/ml and CRP 19.1 mg/dl. Another laboratory control seven hour after surgery showed a WBC count of 25.6/nl, SCr of 2.09 mg/dL, Hb 9 g/dl, Sodium 146 mmol/l, Pot 5.2 mmol/l and Glu <10 mg/dl. The skin became increasingly necrotic. A marked lactate acidosis developed with a pH of seven and a serum lactate concentration over 20 mmol/l with severe microcirculation disturbance. After increasing circulatory and liver failure, palliative therapy was initiated. The patient died 27 h after hospitalization. Blood cultures were positive for Streptococcus pyogenes and Staphylococcus epidermidis. Tissue cultures of the left axilla, elbow and breast demonstrated heavy growth of Streptococcus pyogenes on hospital day three.

The pathological results of the biopsies from the first surgical intervention were available on the eighth day and showed extensive fresh leukocyte demarcated necrosis and skin erosions, most likely corresponding to necrotizing fasciitis. The florid inflammation extended into the muscle. The blood vessels showed signs of fresh thrombosis.

**Microbiological analysis**

Biopsies were incubated in brain heart infusion (BHI, BD, Heidelberg, Germany) for 24 h and subsequently 10 µl BHI were streaked on TSA-, Schaedler-, Choc-, McConkey-, and CNA-Agar (BD, Heidelberg, Germany) by the WASP (Copan). Agar plates were checked for growth at 18 h to 24 h and 42 h to 48 h after inoculation by lab technicians. Identification of all grown colonies were performed by

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**Table 3:** Laboratory results in case 1 at certain time points.

<table>
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<th>24 h</th>
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<tr>
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<tr>
<td>CRP</td>
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<tr>
<td>IL-6</td>
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<tr>
<td>Glu</td>
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**Table 4:** Laboratory results in case 2 at certain time points.

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<td>Glu</td>
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<td>D-Dimer</td>
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**Figure 3:** Superantigen Multiplex PCR: Patterns of 2% agarose gel electrophoresis separation of two multiplex polymerase chain reactions amplifying fragments of all eleven gens coding for superantigens as published by Friães et al. [31].
MALDI-TOF (Bruker, Bremen, Germany) analysis and antimicrobial resistance was tested applying the Phoenix (BD) according to EUCAST standard and breakpoints. Blood cultures were taken in pairs (BD BACTEC™ Plus Anaerobic/F and BD BACTEC™ Lytic/10 Anaerobic/F), sent to the lab and were incubated in the BACTEC FX (BD). Blood cultures were put in the BACTEC immediately after arrival in the lab and instantly streaked out when positive on a 24/7 base.

Gas from both patients were sent for further molecular analysis to the German National Reference Center of Streptococci (Department of Microbiology, University of Aachen, Germany). The MALDI-TOF based species affiliation of the five isolated bacterial strains was verified by β-hemolytic growth on Tryptone Soya Agar with sheep blood (Oxoid, Thermo Scientific) [13], positive Leucyl aminopeptidase (lap) [14] and Pyrrolidonyl peptidase (pyr) [15] test and a positive Lancefield group A-antigen agglutination reaction (Prolex™ Streptococcal Grouping Kit, Pro-Lab Diagnostics) [16], a combination of features solely observed for Streptococcus pyogenes (Table 2).

Further confirmation of the identified bacterial species was addressed by polymerase chain reaction using 'all M primers' [17]. The resulting amplicons were purified using the QIAquick PCR Purification Kit (Qiagen) and sequenced by dyeoxy chain termination cycle sequencing on ABI 3730XL sequencing machines (Eurofins Genomics). The nucleotide sequences were quality trimmed using Chromas (Technelysium Pty Ltd) and emm-types were allotted by StrepBLAST (Streptococcus Laboratory, Centers for Disease Control and Prevention) based on the 180 bp N-terminal hyper-variable regions of the M-protein. This sequence analysis of the emm-gene identified all five isolates as members of the serotype emm89.0. This serotype is frequently isolated from invasive streptococcal infections in Europe [18-23] and described in the context of necrotizing fasciitis [24]. In the last years, a significant increase in invasive S. pyogenes infections with this serotype was observed [25,26]. This perturbing development was linked to the occurrence of a new, very successful genetic clade, associated with the loss of the hyaluronic acid capsule plus increased streptolysin O and NAD-glycohydrolase expression [27]. If the bacterial isolates analyzed here belong to this new S. pyogenes emm89-clade cannot be addressed in this case report, even though an association of this genetic variant with necrotizing fasciitis is suggested [28].

As already mentioned, members of the serotype emm89 are frequently isolated from invasive S. pyogenes infections in Europe. Therefore, the observation that the isolates from both cases belong to the same emm-type and -subtype is not a reliable argument for an infection with the same strain, although all five sequenced 927 bp emm gene fragments are identical. However, for the species S. pyogenes are eleven genes described, which are coding for secreted toxins with superantigen function [29,30], that can be detected by multiplex Polymerase chain reaction (Figure 3, Table 2) [31].

While three of these genes are chromosomally encoded (speG, speL, smez), the remaining eight genes are described to be phage associated (speA, speC, speH, speL, speK, speM, ssa) and therefore their genomic occurrence only loosely linked to the emm type [31]. The observation, that all five isolates from both cases share the same superantigen-gene pattern clearly suggests the hypothesis, that both patients were infected with the same strain.

This argumentation is substantiated by the results of the antibiotics resistance tests, performed by broth microdilution following the guidelines M100 (Performance Standards for Antimicrobial Susceptibility Testing) and M07 (Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically) of the Clinical and Laboratory Standards Institute (Table 2). All five isolates are susceptible for the seven tested antibiotics with slightly elevated minimal inhibitory concentrations for tetracycline and levofloxacin and hence within the range of invasive S. pyogenes isolates in Germany [32]. It can therefore be said, that a familial transmission from one patient to the other resulting in an infection with the same S. pyogenes emm89.0 strain provides a logical explanation for the observed cases.

Discussion

Besides a case of necrotizing fasciitis of the lower leg, which required several revisions, we describe a case leading to the early onset of shock and organ failure with the isolation of Streptococcus pyogenes on culture. In the literature there are only a few reports of clusters of acute life-threatening infections caused by Streptococcus pyogenes in two or more patients [9,12]. However, some studies show an increased risk of GAS transmission in households with mothers and neonates during the neonatal period and in households with couples over 75 years [33]. An explanation for these rare reports of clustering life-threatening GAS infections is not fully given, but serious GAS infections are per se a rare event and a transmission of soft-tissue infections is of considerable low efficiency, especially in a society with a high standard of hygiene. Other diseases caused by GAS, such as pharyngitis, show a higher risk of transmission by droplet infection in asymptomatic or symptomatic pharyngeal carriage. In most cases of familial or nosocomial transmission all contacts had oropharyngeal specimens in culture [11,34,35]. However, the carriers not only show evidence of the pathogen in the throat, but often also vaginally, rectally or in already existing skin lesions [11,35]. In some cases, transmission of invasive GAS has been detected due to nosocomial infections after surgeries performed in the same operating room or contact with the same therapist and a patient to health care worker infection has also been described [36]. In most cases a throat colonization of a health care worker was detected [11,12,37]. These cases bring up the question for the establishment of a general screening regime, a prophylactic therapy or even a vaccination strategy. Both patients were isolated according to the hygiene guidelines. Unfortunately, throat, rectum or vagina culture samples were not taken. Clinical trials testing a streptococcal screening and prophylaxis with benzathine penicillin of GAS carriers showed a decrease in scarlet fever, acute rheumatic fever and acute glomerulonephritis [12,38]. However, international guidelines for the prophylaxis of necrotizing fasciitis vary from country to country [39], but penicillin is generally considered very effective against Streptococcus pyogenes and is also inexpensive [12].

In a situation, where a high incidence of nosocomial or familial infections of invasive GAS infections is detected, active screening may be indicated. Throat and vaginal samples should also be taken to ensure increased sensitivity. Antimicrobial prophylaxis for family members, health care workers or persons in close contact could be justified [12]. Vaccines are currently only in the experimental stage. In particular, work is underway on a general vaccination against GAS to prevent rheumatic fever, rheumatic heart disease and uncomplicated pharyngitis, but there is also the potential in a development to prevent necrotizing fasciitis [40-42]. However, the vaccine would most likely not be able to protect against all serotypes.
that are described to cause necrotizing fasciitis. A general vaccine regime that is also able to prevent the outbreak of necrotizing fasciitis will not be available in the next ten years.

Recent works investigate the possibility of active and passive immunization with the streptococcal surface protein C5a peptidase [43]. Some results suggest, that a parenteral vaccination with an inactive form of the C5a peptidase is able to mediate immunization against group A and B streptococci [40,44]. C5a peptidase is also used in the experimental vaccine Combi5, in combination with streptolysin O, arginine deiminase, trigger factor TF and the interleukin-8 protease SpyCEP [42]. The vaccine shows antibody responses against all administered antigens and mediates a reduction of pharyngitis and tonsillitis infections in a primate model [42]. Several papers present Group A streptococcal M protein-based vaccines [45,46] and vaccines based on recombinant M protein expressed on the surface of a Lactobacillus as carrier [47]. The development of the so-called StreptInCor peptide represents a potent and safe candidate for a universal vaccine epitope in different animal models. The peptide contains fragments of the C-terminal part of the M protein and binds to different HLA class II molecules [41,48,49]. However, there is the possibility of a cross reaction between the antibodies and human proteins, which leads to an autoimmune response induced by these M protein-based vaccines [50,51].

The most important part of the treatment of necrotizing fasciitis is the time factor. An early diagnosis, effective antibiotic treatment and radical surgical intervention are essential for the outcome. In case 1 the first presentation in the department of plastic surgery took place two hours after hospitalization and the following operation ten hours later. In case 2, which showed a much more aggressive progress, the patient presented with a suspected acute coronary syndrome within a known tachyarrhythmia absoluta. Because of the cardiac referral diagnosis, the first presentation in the department of plastic surgery and the rapid surgical intervention took place with a delay of 14 h after hospitalization. This mentioned delay in surgical treatment could be the reason for the further course of the infection. Several studies show that a delay until initial debridement is the main reason for an increase in mortality in necrotizing fasciitis [52,53]. Some authors describe a nine-fold increased risk of death if the initial surgical treatment is delayed by more than 24 h [53]. Despite the surgical interventions with debridement, both patients received massive antibiotic treatment, high volume substitution and catecholamines and administration of blood products as well as coagulation products within an invasive monitoring in the intensive care unit. The surgical debridement or incisional drainage is the most essential part, but there are other management options, which were not used in our cases. One of these adjunctive therapies is Hyperbaric Oxygen Treatment (HBO). In Germany the possibility of this therapy has been known for over 20 years [54]. However, the use of this treatment is discussed controversially. In particular, a positive effect is described for anaerobic clostridial necrotizing fasciitis. In some studies, it is postulated that HBO increases tissue oxygenation in both healthy and diseased tissue. This prevents further spread of the disease, and less debridement is necessary. It is also suspected that bactericidal action of phagocytic cells of the innate immune system like neutrophils is stimulated by HBO treatment [55-57]. Another advantage, which leads to faster wound healing, is the assumption that HBO therapy stimulates neovascularization. Furthermore, oxygenation improves the effect of certain antibiotics such as penicillins, vancomycin, and clindamycin [57,58]. It is also worth mentioning that there are only a few hospitals with easy access to HBO units. According to the Society for Diving and Hypertension Medicine Germany, there are currently 12 hospitals with HBO units in Germany. The patient in case 2 was too unstable to be transported. However, the possible advantages are countered by numerous side effects, including pulmonary edema, pneumothorax, oxygen toxicity seizures or barotrauma [57]. Another adjunctive therapy discussed in the context of necrotizing fasciitis is the treatment with Intravenous Immunoglobulins (IVIG). Theoretically, staphylococcal and streptococcal super antigens are neutralized by polyclonal antibodies against the active sites of these bacterial toxins [59]. It was also shown, that IVIG is able to block the function of other secreted GAS toxins and mediates efficient opsonophagocytic killing of the bacterial cells [60]. IVIG is also described to mediate immunomodulatory effects by reducing the plasma levels of tumor necrosis factor and IL-6. Serious side effects are not described if there is no history of anaphylaxis with immunoglobulins [55].

**Conclusion**

This clinical presentation describes a fatal case of rapid and aggressive necrotizing fasciitis with lethal outcome despite treatment according to guidelines without significant delay. In the second case of necrotizing fasciitis with multiple surgical interventions and extensive intensive medical care within a long hospital stay, the patient could be discharged in a rehabilitation clinic and ambulant aftercare. Both patients lived together in one household and were admitted to the hospital separately, but microbiological analysis of the obtained Streptococcus pyogenes isolates suggests an infection with the same bacterial strain. Transmission of necrotizing fasciitis caused by S. pyogenes is a rare event, but should be considered, which may also justify screening and prophylaxis in an advanced society.

**Acknowledgement**

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**References**


