Clinics in Surgery

Research Article
Published: 11 Dec, 2020

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

Hoh M[1], Bollinger T[2], Kelly JL[3], Itzek A[4] and Dolderer JH[1]*

[1]Department of Plastic, Reconstructive, Aesthetic and Hand Surgery, Medical Center, Bayreuth, Germany

[2]Department of Laboratory Medicine, Microbiology and Hospital Hygiene, Medical Center, Bayreuth, Germany

[3]Department of Plastic and Reconstructive Surgery, Galway University Hospital, Galway, Ireland

[4]Department of Medical Microbiology, German National Reference Center on Streptococcal Diseases, University Hospital RWTH Aachen, Aachen, Germany

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 a 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

OPEN ACCESS

Correspondence:
Dolderer JH, MD, PhD, FACS, Department of Plastic, Reconstructive, Aesthetic and Hand Surgery, Medical Center, Bayreuth, Germany,
E-mail: drdolderer@hotmail.com

Received Date: *05 Nov 2020*
Accepted Date: *07 Dec 2020*
Published Date: *11 Dec 2020*

Citation:
Hoh M, Bollinger T, Kelly JL, Itzek A, Dolderer JH. Familial Transmission of Necrotizing Fasciitis Caused by Group a Streptococcus pyogenes. Clin Surg. 2020; 5: 3010.

Introduction

Necrotizing fasciitis is a fulminant 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.

Table 1: Classification by microbial source of infection.

Type I	Most common (80%) Polymicrobial	Clinical presentation as Fournier gangrene
Type II	Often monomicrobial caused by group A *Streptococcus pyogenes*	Associated with toxic shock syndrome
Type III	Monomicrobial caused by *Vibrio spp*. or *Aeromonas spp*.	Uncommon with high rate of mortality
Type IV	Fungal cause by *Candida spp.*	Contaminated wounds or burns

Table 2: Characteristics of the bacterial isolates from the reported necrotising fasciitis cases. Minimal inhibitory concentration for all seven antibiotics is expressed in microgram per milliliter.

	Case 1	**Case 1**	**Case 2**	**Case 2**	**Case 2**
material	blood	fascia (biopsy)	blood	skin (swab)	mamma (biopsy)
hemolysis	β	β	β	β	β
pyr	+	+	+	+	+
lap	+	+	+	+	+
lancefield	A	A	A	A	A
species	*S. pyogenes*	*S. pyogenes*	*S. pyogenes*	*S. pyogenes*	*S. pyogenes*
emm	89.0	89.0	89.0	89.0	89.0
speA	-	-	-	-	-
speC	+	+	+	+	+
speG	+	+	+	+	+
speH	-	-	-	-	-
speI	-	-	-	-	-
speJ	-	-	-	-	-
speK	+	+	+	+	+
speL	-	-	-	-	-
speM	-	-	-	-	-
smeZ	+	+	+	+	+
Ssa	-	-	-	-	-
Erythromycin	≤ 0.120	≤ 0.120	≤ 0.120	≤ 0.120	≤ 0.120
Clindamycin	≤ 0.120	≤ 0.120	≤ 0.120	≤ 0.120	≤ 0.120
Tetracyclin	0.5	0.25	0.5	0.25	0.5
Penicillin	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015
Amoxicillin	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015
Cefotaxime	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015
Levofloxacin	0.5	1	1	1	1

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 on the thigh (Figure 1a and b).

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

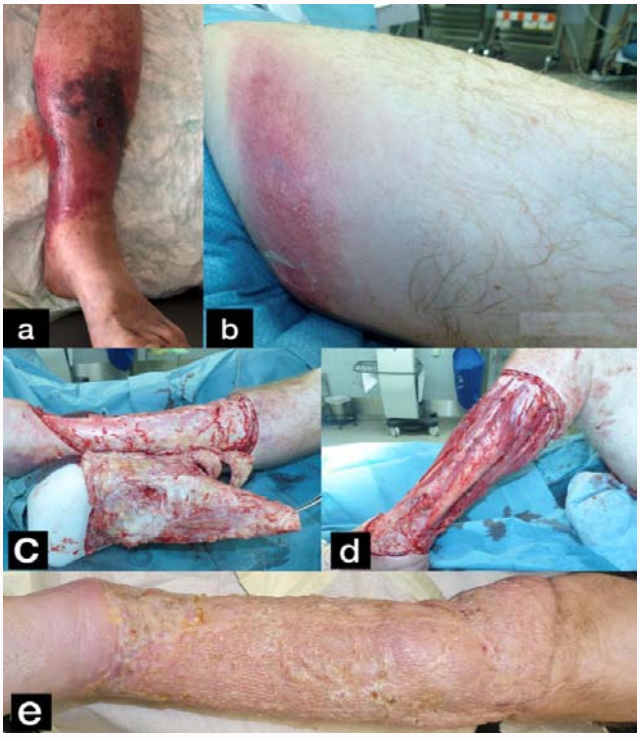

Figure 1: a) Photographic documentation of necrotic lesions of the lower left leg, b) cellulitis ofmedial thigh left, c) and d) necrotising fasciitis of the lower left leg intraoperative, e) and healed soft tissue defect after reconstruction with local flaps and skin graft.

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

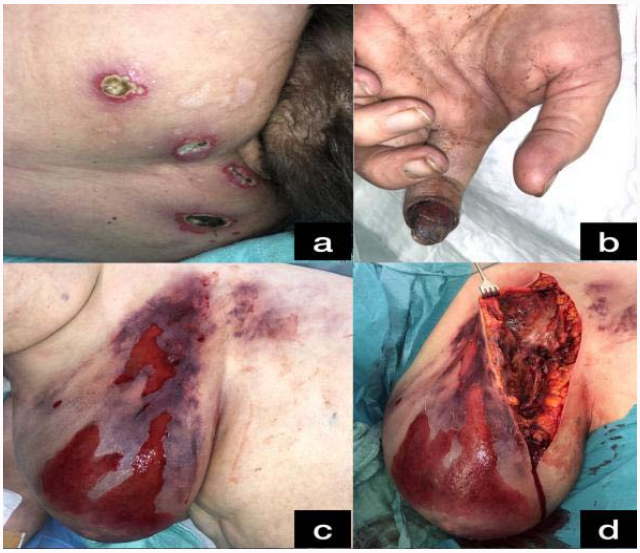

Figure 2: a) Photographic documentation of necrotic lesions on the back, b) dry gangrene on the index finger distal phalanx left hand, c) necrotising fasciitis at the left breast and chest wall preoperative, d) necrotising fasciitis at the left breast and chest wall after incision.

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

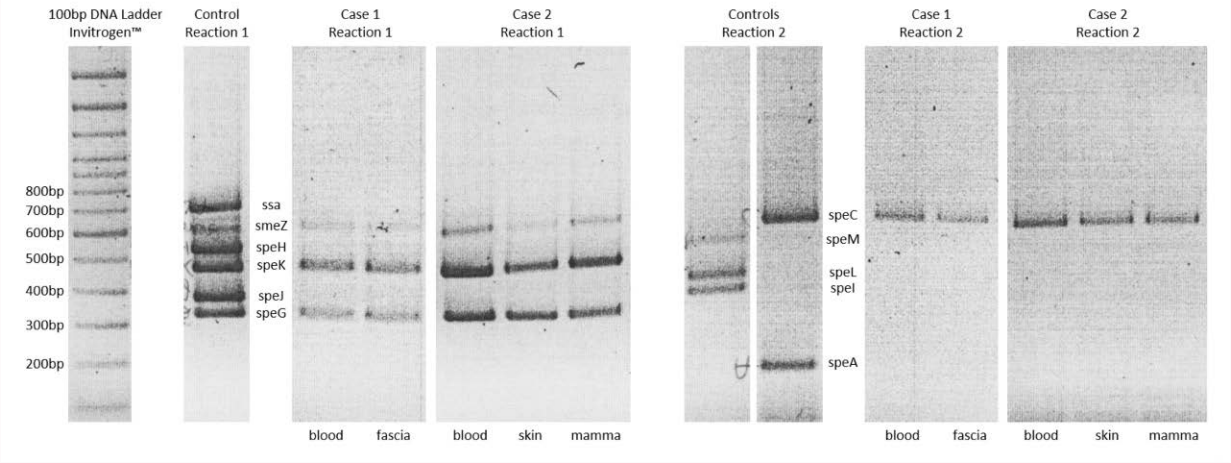

Figure 3: Superantigen Multiplex PCR: Patterns of 2% agarose gel electrophoresis separation of two multiplex polymerase chain reactions amplifying fragments of all eleven gens coding for superantigens as published by Friães et al. [31].

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

Timepoint	0	10 h	24 h	6 days
Temperature	39.3°C			
Blood pressure	80/65 mmHg			
Heart rate	113			
Oxygen saturation	95%			
WBC	15.4/nl	14.9/nl	25.2/nl	43/nl
SCr	2.87 mg/dL	2.67 mg/dL	2.18 mg/dL	1.17 mg/dL
Hb	13.8 g/dl	12.2 g/dl	7.9 g/dl	8.5 g/dl
Sodium	133 mmol/l	136 mmol/l	142 mmol/l	145 mmol/l
PCT	57.55 ng/ml	63.39 ng/ml	62.59 ng/ml	3.90 ng/ml
CRP	23.7 mg/dl	27.3 mg/dl		4.2 mg/dl
IL-6			736.1 pg/ml	
Glu			148 mg/dl	

Table 4: Laboratory results in case 2 at certain time points.

Timepoint	0	10 h	12 h	14 h	19 h
Temperature	36.2°C				
Blood pressure	80/60 mmHg				
Heart rate	144				
Oxygen saturation	80%				
WBC	15.3/nl		14.5/nl	18.5/nl	25.6/nl
SCr	2.6 mg/dL		2.04 mg/dL	1.99mg/dL	2.09 mg/dL
Hb	14.6 g/dl		9.8 g/dl	10.5 g/dl	9 g/dl
Sodium	120 mmol/l		136 mmol/l	136 mmol/l	146 mmol/l
PCT	5.33 ng/ml			6.10 ng/ml	
CRP	40.7 mg/dl		16.5 mg/dl	19.1 mg/dl	
IL-6	14937.0 pg/ml	30708 pg/ml		18562.0 pg/ml	
Glu	79 mg/dl			<10 mg/dl	
D-Dimer	3.73 mg/l				
Potassium					5.2 mmol/l

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

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 Aerobic/F and BD BACTEC™ Lytic/10 Anaerobic/F), send 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 QIAquickl PCR Purification Kit (Qiagen) and sequenced by dideoxy 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*, *speJ*, *smeZ*), the remaining eight genes are described to be phage associated (speA, speC, speH, speI, speK, speL, 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 Combo5, 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

We would like to thank MU Dr. K. Koniarikova for her spadework and the National Reference Centre for the microbiological analysis. We also thank the patients and their relatives who have allowed us to report these cases.

References

1. Cheung JPY, Fung B, Tang WM, Ip WY. A review of necrotising fasciitis in the extremities. Hong Kong Med J. 2009;15(1):44-52.
2. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: A retrospective study. Am Surg. 1998;64(5):397-400; discussion 400-1.
3. Strus M, Heczko PB, Golińska E, TomusiakA, Chmielarczyk A, Dorycka M, et al. The virulence factors of group A *Streptococcus strains* isolated from invasive and non-invasive infections in Polish and German Centers, 2009-2011. Eur J Clin Microbiol Infect Dis. 2017;36(9):1643-9.
4. Watanabe S, Takemoto N, Ogura K, Miyoshi-Akiyama T.Severe invasive *Streptococcal*infection by *Streptococcus pyogenes* and *Streptococcus dysgalactiae*Subsp. Equisimilis. Microbiol Immunol. 2016;60(1):1-9.
5. Lamagni T, Efstratiou A, Vuopio-Varkila J, Jasir A, Schalén C; Strep-EURO. The epidemiology of severe *Streptococcus pyogenes* Associated Disease in Europe. Euro Surveill. 2005;10(9):179-84.
6. LamagniTL, Darenberg J, Luca-Harari B, Siljander T, Efstratiou A, Henriques-Normark B, et al. Epidemiology of severe *Streptococcus pyogenes*disease in Europe. J Clin Microbiol. 2008;46(7):2359-67.
7. Morgan MS. Diagnosis and management of necrotising fasciitis: A multiparametric approach. J Hosp Infect. 2010;75(4):249-57.

8. Schwartz B, Elliott JA, Butler JC, Simon PA, Jameson BL, Welch GE, etal. Clusters of invasive groupA *Streptococcal*infections in family, hospital, and nursing home settings. Clin Infect Dis. 1992;15(2):277-84.

9. GambaMA, Martinelli M, Schaad HJ, Streuli RA, DiPersio J, Matter L, et al. Familial transmission of a serious disease--producing group A *Streptococcus* clone: Case report and review. Clin Infect Dis. 1997;24(6):1118-21.

10. Doyon C, Goodyear E. Case report of the family transmission of *Streptococcus pyogenes*orbital cellulitis. Am J Ophthalmol Case Rep. 2017;6:52-4.

11. Al-ajmi JA, Hill P, O' Boyle C, Basco Garcia ML, Malkawi M, George A, et al. Group A *Streptococcus*toxic shock syndrome: An outbreak report and review of the literature. J Infect Public Health. 2012;5(6):388-93.

12. Ichiyama S, Nakashima K, Shimokata K, Ohta M, Shimizu Y, Ooe K, et al. Transmission of *Streptococcus pyogenes*causing toxic shock-like syndrome among family members and confirmation by DNA macrorestriction analysis. J Infect Dis. 1997;175(3):723-6.

13. Brown JH. The use of blood agar for the study of *Streptococci*. Monographs of the RIMR., 1919.

14. Colman G, Ball LC. Identification of *streptococci* in a medical laboratory. J Appl Bacteriol. 1984;57(1):1-14.

15. Kaufholdt A, Luttickent R, Schwien U. Few-minutes tests for the identification of group A *Streptococci* and *Enterococci* with chromogenic substrates. ZentralblBakteriol. 1989;272(2):191-5.

16. Lancefield RC. A serological differentiation of human and other groups of hemolytic *Streptococci*. J Exp Med. 1933;57(4):571-95.

17. Podbielski A, Melzer B, Lütticken R. Application of the polymerase chain reaction to study the M protein(-like) gene family in beta-hemolytic streptococci. Med Microbiol Immunol. 1991;180(4):213-27.

18. Darenberg J, Luca-Harari B, Jasir A, Sandgren A, Pettersson H, Schalén C, et al. Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. Clin Infect Dis. 2007;45(4):450-8.

19. Imöhl M, van der Linden M, Reinert RR, Ritter K. Invasive group A streptococcal disease and association with varicella in Germany, 1996-2009. FEMS Immunol Med Microbiol. 2011;62(1):101-9.

20. Plainvert C, Loubinoux J, Bidet P, Doloy A, Touak G, Dmytruk N, et al. [Epidemiology of *Streptococcus* pyogenes invasive diseases in France (2007-2011)]. Arch Pediatr. 2014;21(Suppl 2):S62-8.

21. Lambertsen LM, Ingels H, Schønheyder HC, Hoffmann S; Danish Streptococcal Surveillance Collaboration Group 2011. Nationwide laboratory-based surveillance of invasive beta-haemolytic streptococci in Denmark from 2005 to 2011. Clin Microbiol Infect. 2014;20(4):O216-23.

22. Friães A, Melo-Cristino J, Ramirez M; Portuguese Group for the Study of Streptococcal Infections. Changes in emm types and superantigen gene content of Streptococcus pyogenes causing invasive infections in Portugal. Sci Rep. 2019;9(1):18051.

23. Grivea IN, Syrogiannopoulos GA, Michoula AN, Gazeti G, Malli E, Tsilipounidaki K, et al. emm Types and clusters and macrolide resistance of pediatric group A streptococcal isolates in central Greece during 2011-2017. PLoS One. 2020;15(5):e0232777.

24. Inoue M, Kako E, Kinugasa R, Sano F, Iguchi H, Sobue K. Necrotizing fasciitis following primary peritonitis caused by *Streptococcus pyogenes* with covS mutation in a healthy woman: A case report. JA Clin Rep. 2019;5(1):29.

25. Turner CE, Abbott J, Lamagni T, Holden MTG, David S, Jones MD, et al. Emergence of a new highly successful a capsular Group A *Streptococcus*clade of genotype emm89 in the United Kingdom. mBio. 2015;6(4):e00622.

26. Friães A, Machado MP, Pato C, Carriço J, Melo-Cristino J, Ramirez M. Emergence of the same successful clade among distinct populations of emm89 *Streptococcus pyogenes* in multiple geographic regions. mBio. 2015;6(6):e01780-15.

27. Zhu L, Olsen RJ, Nasser W, de la Riva Morales I, Musser JM. Trading capsule for increased cytotoxin production: Contribution to virulence of a newly emerged clade of emm89 *Streptococcus pyogenes*. mBio. 2015;6(5):e01378-15.

28. Teatero S, Coleman BL, Beres SB, Olsen RJ, Kandel C, Reynolds O, et al. Rapid emergence of a new clone impacts the population at risk and increases the incidence of type emm89 group A *Streptococcus*invasive disease. Open Forum Infect Dis. 2017;4(2):ofx042.

29. Kotb M. Bacterial pyrogenic exotoxins as superantigens. Clin Microbiol Rev. 1995;8(3):411-26.

30. Sriskandan S, Faulkner L, Hopkins P.*Streptococcus pyogenes*: Insight into the function of the streptococcal superantigens. Int J BiochemCell Biol. 2007;39(1):12-9.

31. Friães A, Pinto FR, Silva-Costa C, Ramirez M, Melo-Cristino J. Superantigen gene complement of *Streptococcus pyogenes*--relationship with other typing methods and short-term stability. Eur J Clin Microbiol Infect Dis. 2013;32(1):115-25.

32. Imöhl M, van der Linden M. Antimicrobial susceptibility of invasive *Streptococcus pyogenes*isolates in Germany during 2003-2013. PLoS One. 2015;10(9):e0137313.

33. Mearkle R, Saavedra-Campos M, Lamagni T, Usdin M, Coelho J, Chalker V, et al. Household transmission of invasive group A *Streptococcus* infectionsin England: A population-based study, 2009, 2011 to 2013. Euro Surveill. 2017;22(19):30532.

34. Mazón A, Gil-Setas A, Sota de la Gándara LJ, Vindel A, Sáez-Nieto JA. Transmission of *Streptococcus pyogenes*causing successive infections in a family. Clin Microbiol Infect. 2003;9(6):554-9.

35. Stamm WE, Feeley JC, Facklam RR. Wound infections due to group A *Streptococcus*traced to a vaginal carrier. J Infect Dis. 1978;138(3):287-92.

36. Montes M, Tamayo E, Oñate E, Pérez-YarzaEG, Pérez-Trallero E. Outbreak of *Streptococcus pyogenes*infection in healthcare workers in a Paediatric Intensive Care Unit: Transmission from a single patient. Epidemiol Infect. 2013;141(2):341-3.

37. Talbot TR, May AK, Obremskey WT, Wright PW, Daniels TL. Intraoperative patient-to-healthcare-worker transmission of invasive group A streptococcal infection. Infect Control Hosp Epidemiol. 2011;32(9):924-6.

38. Thomas RJ, Conwill DE, Morton DE, Brooks TJ, Holmes CK, Mahaffey WB. Penicillin prophylaxis for streptococcal infections in United States Navy and Marine Corps Recruit Camps, 1951-1985. Rev Infect Dis. 1988;10(1):125-30.

39. Kaul R, McGeer A, Low DE, Green K, Schwartz B. Population-based surveillance for group A streptococcal necrotizing fasciitis: Clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases. Ontario group A streptococcal study. Am J Med. 1997;103(1):18-24.

40. Cleary PP, Matsuka YV, Huynh T, Lam H, Olmsted SB. Immunization with C5apeptidase from either group A or B streptococci enhances clearance of group A streptococci from intranasally infected mice. Vaccine. 2004;22(31-32):4332-41.

41. Guilherme L,Ferreira Fm, Köhler KF, Postol E, Kalil J. A heart disease. Am J Cardiovasc Drugs. 2013;13(1):1-4.

42. Rivera-Hernandez T, Carnathan DG, Jones S, Cork AJ, Davies MR, Moyle PM, et al. An experimental group A *Streptococcus*vaccine that reduces pharyngitis and tonsillitis in a nonhuman primate model. M Bio. 2019;10(2):e00693-19.

43. Park HS, Cleary PP. Active and passive intranasal immunizations with streptococcal surface protein C5a peptidase prevent infection of murine nasal mucosa-associated lymphoid tissue, a functional homologue of

human tonsils. Infect Immun. 2005;73(12):7878-86.

44. Shet A, Kaplan EL, Johnson DR, Cleary PP. Immune response to group A streptococcal C5a peptidase in children: Implications for vaccine development. J Infect Dis. 2003;188(6):809-17.

45. Hu MC, Walls MA, Stroop SD, Reddish MA, Beall B, Dale JB. Immunogenicity of a 26-valent Group A streptococcal vaccine. Infect Immun. 2002;70(4):2171-7.

46. Dale JB, Smeesters PR, Courtney HS, Penfound TA, Hohn CM, Smith JC,et al. Structure-based design of broadly protective group a Streptococcal M protein-based vaccines. Vaccine. 2017;35(1):19-26.

47. PiardJC, Hautefort I, Fischetti VA, Ehrlich SD, Fons M, Gruss A. Cell wall anchoring of the *Streptococcus pyogenes* M6 protein in various lactic acid bacteria. J Bacteriol. 1997;179(9):3068-72.

48. Guilherme L, Postol E, Ferreira FM, DeMarchi LMF, Kalil J. StreptInCor: A model of anti-*Streptococcus pyogenes* vaccine reviewed. Auto Immun Highlights. 2013;4(3):81-5.

49. Guilherme L, Alba MP, Ferreira FM, Oshiro SE, Higa F, Patarroyo ME, et al. Anti-group A streptococcal vaccine epitope: Structure, stability, and its ability to interact with HLA class II molecules. J Biol Chem. 2011;286(9):6989-98.

50. Azuar A, Jin W, Mukaida S,Hussein WM, Toth I, Skwarczynski M. Recent advances in the development of peptide vaccines and their delivery systems against group A *Streptococcus*. Vaccines (Basel). 2019;7(3):58.

51. Cooper JA, Hayman W, Reed C, Kagawa H, Good MF, Saul A. Mapping of conformational B cell epitopes within alpha-helical coiled coil proteins. Mol Immunol. 1997;34(6):433-40.

52. Rac H, Bojikian KD, Lucar J, Barber KE. Successful treatment of necrotizing fasciitis and streptococcal toxic shock syndrome with the addition of linezolid. Case Rep Infect Dis. 2017;2017:5720708.

53. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: Clinical presentation, microbiology, and determinants of mortality. J Bone Joint Surg Am. 2003;85(8):1454-60.

54. Podbielski A, Rozdzinski E, Wiedeck H, Lütticken R. Gruppe A Streptokokken und die nekrotisierendeFasziitis. Dtsch. Ärzteblatt. 1998;95(8):A-414/B-350/C-326.

55. Korhonen K. Hyperbaric oxygen therapy in acute necrotizing infections with a special reference to the effects on tissue gas tensions. Ann ChirGynaecol Suppl. 2000;(214):7-36.

56. Escobar SJ, SladeJr JB, Hunt TK, Cianci P. Adjuvant hyperbaric oxygen therapy (HBO2)for treatment of necrotizing fasciitis reduces mortality and amputation rate. Undersea Hyperb Med. 2005;32(6):437-43.

57. MacFarlane C, Cronje FJ, Benn CA. Hyperbaric oxygen in trauma and surgical emergencies. J R Army Med Corps. 2000;146(3):185-90.

58. Wilkinson D, Doolette D. Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. Arch Surg. 2004;139(12):1339-45.

59. Norrby-TeglundA, Kaul R, Low DE, McGeer A, Andersson J, Andersson U, et al. Evidence for the presence of streptococcal-superantigen-neutralizing antibodies in normal polyspecific immunoglobulin G. Infect Immun. 1996 Dec;64(12):5395-8.

60. Babbar A, Bruun T, Hyldegaard O, Nekludov M, Arnell P;mINFECT Study Group, et al. Pivotal role of preexisting pathogen-specific antibodies in the development of necrotizing soft-tissue infections. J Infect Dis. 2018;218(1):44-52.