Going Out on a Limb

Do Not Delay Diagnosis of Necrotizing Fasciitis in Varicella Infection

Jonathan P. Sturgeon, MBBS, Laura Segal, MBBS,† and Anita Verma, MBBS‡*

Abstract: Necrotizing fasciitis (NF) is a rare complication of varicella zoster (chicken pox) infection. Its diagnosis can be delayed or missed, which increases mortality and morbidity, because it initially presents similarly to cellulitis. We present the case of a 5-year-old boy who presented with a swollen leg, the difficulties in the diagnosis of NF, and a review of the literature. Necrotizing fasciitis complicating varicella zoster in children is associated with 3.4% mortality, although this rises to 13.6% in streptococcal toxic shock syndrome. Seventy-one percent of cases are confirmed as being caused by group A β-hemolytic *Streptococcus*. The association of NF with chicken pox is discussed along with the difficulties in diagnosis and treatment options. Necrotizing fasciitis is a surgical emergency and should be considered by all emergency department acute care practitioners in cases of varicella in which fever is enduring and swelling or pain is disproportionate. Because of the difficulty in diagnosis, senior opinion should be sought early.

Key Words: necrotizing fasciitis, varicella zoster, chicken pox, streptococcal toxic shock, group A β-hemolytic *Streptococcus*

(*Pediatr Emer Care* 2015;31: 503–507)

Necrotizing fasciitis (NF) is a serious bacterial infection that spreads rapidly and destroys the body's soft tissue. This rare disease can be caused by more than 1 type of bacteria. These include group A β-hemolytic *Streptococcus* (GABHS), *Klebsiella*, *Clostridium*, *Escherichia coli*, *Staphylococcus aureus,* and *Aeromonas hydrophila*, among others. Group A β-hemolytic *Streptococcus* is considered to be the most common cause of NF. Accurate diagnosis and prompt treatment with antibiotics are important, and early surgery is vital. We report the difficulty in diagnosing NF and discuss optimal medical and surgical treatment as well as a review of the literature for NF after varicella zoster infection in children.

CASE

A previously healthy 5-year-old boy was referred by a primary care physician to the emergency department with a suspicion of a lower limb deep vein thrombosis on a background of varicella zoster infection. The parents had noted his chicken pox rash 4 days previously. The rash was diffuse with vesicles that had since crusted, and no new lesions had cropped for 24 hours.

On the evening before presentation, he complained of left leg pain and started to have difficulty weight bearing, but nothing was noted on examination by the parents. On the morning of presentation, a bruise on the medial aspect of his left calf was noted, where there was a healing chicken pox lesion. During the course of the morning, the calf became very swollen, and the "bruise" became larger and darker. He had developed fevers 24 hours before presentation associated with lethargy, reduced fluid intake, and reduced urine output.

On examination, the patient was very quiet and looked unwell; he was febrile at 38.8°C after administration of paracetamol, his heart rate was 120 beats per minute, and his blood pressure was 98/55 mm Hg. His peripheral capillary refill time was 2 seconds, but he had dry mucous membranes with very cracked lips. His left leg was grossly swollen, and the knee, the calf, and the ankle were erythematous and tense. There was a 4 × 3-cm dark purple patch on the medial calf, with a central punctum of a resolving varicella lesion. The midcalf circumference was 3 cm larger on the left at 27.5 cm; there was no difference in the thigh circumferences. There was extreme pain on passive movement of the ankle and the knee. The limb was neurovascularly intact.

Initial blood results revealed a sodium of 124 mmol/L, urea of 9.9 mmol/L, and creatinine of 61 μmol/L. C-reactive protein was 80 mg/L, with a white cell count of 8.7×10^9/L, platelet count of 136×10^9/L, and a lactate of 2.5 mmol/L. An ultrasound of the leg showed subcutaneous edema with localized hyperemia. He was initially given intravenous flucloxacillin and ceftriaxone as well as maintenance intravenous fluids. An orthopedic review suggested that he did not have compartment syndrome as well as to elevate the leg and to await senior orthopedic review the next morning.

During the next 12 hours, he continued to spike fevers, he became more tachycardic, and his blood pressure dropped to 66 mm Hg systolic despite six 10-mL/kg intravenous fluid boluses. Antibiotics were changed to meropenem, vancomycin, and gentamicin, and clindamycin was added in later. On the next morning after admission, he went to the theater for a 2-incision fasciotomy and debridement of the posterior superficial compartment of the left leg (Fig. 1). The ischemic area had grown to 10 × 15 cm.

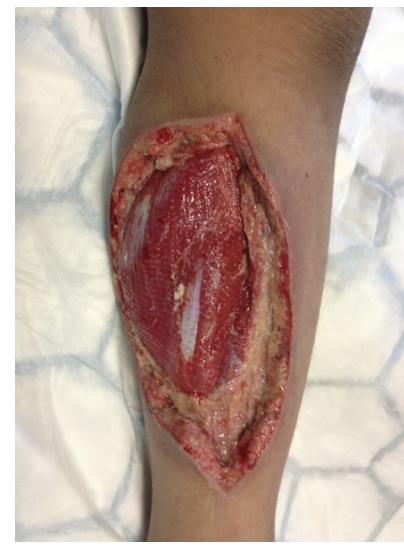

FIGURE 1. The patient's leg after the first debridement.

From the *Emergency Department, †Department of Paediatrics, and ‡Department of Microbiology, King's College Hospital, London, UK.
Disclosure: The authors declare no conflict of interest.
Reprints: Jonathan Sturgeon, MA, MBBS, King's College Hospital, Denmark Hill, London, SE5 9RS UK (e-mail: jonathan.sturgeon@nhs.net).

ISSN: 0749-5161

TABLE 1. Reported Cases of NF With Preceding VZV infection

Case/Study	Date	No. Cases	Mean Age	Male, %	Infective Organism	Streptococcal Toxic Shock	Survival, %	Day of Varicella Admitted
Sturgeon et al	2014	1	5	100	GABHs (100%)	100%	100	4
Li and Xia[11]	2012	1	7	0	GABHs (100%)	100%	100	6
Shirley et al[5]	2011	1	2.75	0	GABHs (100%)	100%	100	5
Chan et al[12]	2010	1	4	0	GABHs (100%)	100%	100	1
Sablier et al[13]	2010	1	0.75	0	GABHs (100%)	100%	100	—
Minodier et al[14]	2009	10	*4.9*	*50*	GABHs (100%)	*33%*	*90*	—
Minodier et al[15]	2008	1	3	0	GABHs (100%)	100%	0	7
Ekingen et al[16]	2008	1	1.4	0	Unknown	0%	100	—
de Benedictis and Osimani[17]	2008	1	2	0	GABHs (100%)	0%	100	—
Sharma et al[18]	2008	1	5	100	Unknown	0%	100	—
Bingöl-Koloğlu et al[19]	2007	6	6.4	33	GABHs (50%), *Staphylococcus epidermidis* (17%), unknown (33%)	Unknown	100	—
Bhat et al[20]	2007	5	3.4	60	GABHs + *S. aureus* (20%), *S. aureus* (20%), *Streptococcus* species (20%), *Pseudomonas* species (20%), group A *Streptococcus* + *S. aureus* (20%)	40%	80	—
Eneli and Davies[21]	2007	1	0.9	100	GABHs (100%)	0%	100	—
Hidalgo-Carballal and Suárez-Mier[22]	2006	1	4	100	GABHs (100%)	100%	100	5
Griffith et al[23]	2005	1	1.3	0	*S. aureus* (100%)	0%	100	4
Kurekci et al[24]	2005	1	4	0	GABHs (100%)	0%	100	4
Patel et al[25]	2004	7	7.57	43	GABHs (100%)	71%	100	—
Vijaykumar et al[26]	2003	5	2.2	80	*Streptococcus pneumoniae* with *Peptostreptococcus* (20%), *S. aureus* (20%), *E. coli* (20%), Coagulase-negative staphylococci (20%), unknown (20%)	0%	100	6, 6, 4, 6, 7
Clark et al[27]	2003	5	3.8	60	GABHs (80%), unknown (20%)	40%	100	6, 7, 1, 7, 5
Fustes-Morales et al[28]	2002	13	2.6	54	Unknown (38%), mixed (31%), *Enterococcus faecium* (15%), GABHs (8%), α-hemolytic *Streptococcus* (8%)	0%	100	—
Guneren et al[29]	2002	1	1.25	100	Unknown	0%	100	3
Ziebold et al[30]	2001	3	—	100	GABHs (100%)	Unknown	100	—
Slack et al[31]	2000	1	8	100	GABHs (100%)	0%	100	3
Zerr et al[7]	1999	19	4.6	74	GABHs (84%), others (*S. aureus*, *Haemophilus influenzae*, group B streptococci) (10%), none (5%)	26%	100	—
Lin et al[32]	1998	2	4	0	GABHs (100%)	0%	100	4
Zurawski et al[33]	1998	1	7	—	—	—	0	—
Givner[34]	1998	1	1	0	GABHs (100%)	100%	100	—
Moss et al[35]	1996	5	—	≤80	GABHs (20% mortality case) (80%)	Unknown	80	—
Schreck et al[36]	1996	5	2.2	80	GABHs (80%), unknown (20%)	40%	100	—
Aebi et al[37]	1996	4	*2.9*	Unknown	GABHs (75%), unknown (25%)	Unknown	Unknown	—
Waldhausen et al[38]	1996	18	*4.5*	68	GABHs (78%), *S. aureus* (11%), unknown (11%)	33%	100	—
Mills et al[39]	1996	1	10	100	GABHs (100%)	100%	100	7
Vugia et al[40]	1996	1	0.6	100	GABHs (100%)	0%	100	4
Brogan et al[9]	1995	14	4.3	29	GABHs (100%)	36%	100	2–6
Wilson et al[41]	1995	4	5.75	50	GABHs (100%)	Unknown	100	4, 7, 9, 5
Molea et al[42]	1994	1	7	100	—	0%	100	"Few days"
Zittergruen and Grose[43]	1993	1	6	100	GABHs (100%)	0%	100	7

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TABLE 1. *(Continued)*

Case/Study	Date	No. Cases	Mean Age	Male, %	Infective Organism	Streptococcal Toxic Shock	Survival, %	Day of Varicella Admitted
Schwarz et al[44]	1989	1	2	100	Gram-positive cocci (100%)	100%	100	7
Falcone et al[45]	1988	1	8	0	GABHS (100%)	100%	100	7
Kyong et al[46]	1985	2	0.7	100	GABHS (50%), *S. aureus* (50%)	0%	100	4, 5
Total		150	Mean age, 4.2 y	83/140 (59%)	GABHS 102/143 (71.3%)	41/108 (37%)	141/146 (96.6%)	Mean, 4.7 d

Method: search of MEDLINE and EMBASE with the terms *necrot** adjacent to *fasc** or *subject: necrotizing fasciitis*. The results were reduced to those that also had *subject: chickenpox* or the words *varicella* or *zoster* anywhere in the text. Any results not in English were removed. Patients older than 16 years were removed. Studies in which cases of NF in VZV could not be partially separated from other results were removed. Three results in which NF in VZV could not be fully separated from larger groups have been shown, with the results for the larger groups in *italics* in the table.

Em dash denotes not mentioned in the article.

There was foul-smelling fluid and tissues were initially dull but pink on debridement, indicative of NF.

Wound swabs and blood cultures grew GABHS. He required inotropes and intravenous fluids to maintain his blood pressure and was intubated and ventilated for 6 days. He returned to the theater for a further debridement and a subsequent split skin graft, which maintained good limb function. Intravenous antibiotics were continued for a total of 13 days, and he was discharged home after a total of 16 days of admission.

DISCUSSION AND REVIEW

Varicella zoster virus (VZV) is a common herpes virus that causes chicken pox in children and young adults. It is a common and highly contagious virus, infecting up to 90% of people who come into contact with the disease. More than 90% of people are seropositive by 20 years of age.[1] Bacterial superinfection of chicken pox lesions is considered to be a common acute complication, usually leading to a mild soft tissue infection, or cellulitis. Rarely, however, bacterial infection can cause rapidly progressing necrosis of the fascia and soft tissue (including the skin and the muscle), which is characteristic of NF, popularized by the tabloid press as "flesh-eating bacteria."[2]

Necrotizing fasciitis has been classified as polymicrobial (type 1) or caused by GABHS with or without a *Staphylococcus* (type 2).[3] Varicella zoster virus infection is a significant risk factor of NF, with 50% of 1 case series having chicken pox as the initiating factor.[4] Varicella zoster virus infection increases the risk for invasive GABHS infection by 58-fold.[4] In adults, other risk factors include diabetes, steroid use, and immunocompromise; however affected children usually have no comorbidities.[5]

The association between GABHS and VZV infection is increasing: according to 1 study between 1977 and 1992, a total of 7% of GABHS infections were associated with VZV infection; in 1993, a total of 50% of new GABHS infections were in children with VZV infection.[6] It has been suggested that changes in the infectivity or virulence of the organism may account for this change.[2] The association between VZV and varicella is not well understood, but it is suggested that the varicella infection disrupts the protective skin layer, allowing bacteria to enter. Varicella zoster virus infection can also switch helper T cells from a T_H2 to a T_H1 dominant subtype in patients with atopic dermatitis. T_H2 cells promote humoral immunity, and the immunomodulatory effect associated with this decreased humoral immunity may be important in bacterial infection.[4] The suggestion has been made that there could be a link between nonsteroidal anti-inflammatory drug use and GABHS infection in VZV. One study showed a link, but 7 of 9 of their cases had taken the nonsteroidal anti-inflammatory drug after the onset of NF.[7] Other studies have not demonstrated a link.[8,9] Data are therefore insufficient to make a link.[10]

A literature search revealed a total of 150 cases of NF after VZV infection in children (Table 1). The mean age was 4.2 years (range, 0.6-10 years), with 59% of the patients being boys. Group A β-hemolytic *Streptococcus* was the commonest organism identified, representing 71% of cases. Mortality was 3.4%. The children were admitted to the hospital a mean of 4.7 days after eruption of the VZV rash (n = 45; range, 1-9 days).

Thirty-seven percent of the cases presented with additional hypovolemia and systemic shock. These cases, along with our patient, fulfill the criteria for streptococcal toxic shock syndrome (STSS) (Table 2). In STSS, high concentrations of inflammatory cytokines disturb microcirculation and lead to hypotension, shock, and organ failure.[15] The pathogenesis is poorly understood, but exotoxins produced by the bacteria (streptococcal pyrogenic exotoxin A and streptococcal pyrogenic exotoxin B), acting as superantigens, as well as M-type proteins in the bacterial wall play a part.[15,47,48] The mortality associated with STSS complicating NF was considerably higher at 13.6%, and the children tended

TABLE 2. Diagnostic Criteria for STSS[10]

I. Isolation of GABHS
- A. From a normally sterile site (eg, blood, cerebrospinal fluid, peritoneal fluid, tissue biopsy specimen)
- B. From a nonsterile site (eg, throat, sputum, vagina)

II. Clinical Signs of Severity
- A. Hypotension: systolic blood pressure ≤ 90 mm Hg in adults or ≤5th percentile for age in children and
- B. Two or more of the following signs:
  1. Renal impairment, creatinine ≥ 2 mg/dL (176.8 μmol/L) for adults or more than twice the upper limit of normal for age
  2. Coagulopathy: platelet count ≤ 100,000/μL or disseminated intravascular coagulation
  3. Hepatic involvement: alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), or total bilirubin levels twice or more than the upper limit of normal for age
  4. Adult respiratory distress syndrome
  5. A generalized erythematous macular rash that may desquamate
  6. Soft tissue necrosis, including NF or myositis, or gangrene

An illness fulfilling criteria IA and II (A and B) can be defined as a definite case. An illness fulfilling criteria IB and II (A and B) can be defined as a probable case if no other cause for the illness is identified.

to be older, with a mean age of 4.4 years compared with 3.2 years in those without STSS ($P = 0.05$).

Difficulty in diagnosis, as noted in our case, is a well-recognized problem because early NF can be indistinguishable from cellulitis and erysipelas.[45,49] Necrotizing fasciitis in children is not common, at an estimated incidence of 0.05 to 0.21 per 100,000 children per year,[4,21,50] so clinicians are unlikely to have extensive experience in dealing with the condition. The classic "triad" of symptoms is exquisite pain out of proportion to the clinical findings, swelling, and fever.[49,51] Late signs are hemorrhagic bullae, skin anesthesia, crepitations, and skin necrosis.[51] Further difficulty diagnosing can occur because VZV infection causes fever for the first 48 hours,[38] and young children may find it difficult to communicate ongoing pain levels.

Ultrasound may be useful in diagnosing NF, especially when differentiating from cellulitis, showing fluid accumulation in the fascial plane.[52] Computed tomography and magnetic resonance imaging have also been used to rule out cellulitis,[10,52] but radiation exposure and magnetic resonance imaging availability may limit these modalities. Surgery is often the only way to confirm a diagnosis of NF. A low index of suspicion and early senior surgical input are therefore of utmost importance because inexperienced juniors can be put off by lack of necrosis or blistering in early NF.[53] A scoring system to identify patients with NF has been developed, but it has not been validated in children.[54]

Treatment of NF is with fluid resuscitation, antibiotics, and early surgical debridement of necrotic tissue. For GABHS, antibiotics are usually penicillin G, dependent on sensitivities, with added clindamycin because it has an antiexotoxin effect.[9,10] The bacterial exotoxins can destroy soft tissue and reduce blood flow, so antibiotics may not reach all of the infected and decaying areas. This could explain why, despite antibiotics, our patient's necrotic tissue area increased more than 10-fold in less than 24 hours. Rapid surgical removal of dead tissue with clear margins is therefore critical to managing the infection. Esthetic considerations must be secondary because incomplete debridement is a major risk factor of further complications.[26] Delay in initial debridement worsens patient outcome; in 1 report, good outcome was noted in all 15 children who underwent aggressive surgical debridement within 3 hours.[35]

CONCLUSIONS

Although chicken pox is common and self-limiting, it can be complicated by NF, which results in a mortality of 3.4%. Seventy-one percent of cases are confirmed to be caused by GABHS. Early senior surgical involvement is vitally important because surgical debridement is the only definitive treatment and can prevent loss of limbs and mortality. Complication with or progression to STSS complicates 37% of NF infections in VZV, with a 4-fold increase in mortality rate. Because it is rare and not a commonly thought of complication of VZV, clinicians generally have limited experience of NF and may not have a high index of suspicion. Luckily, our patient has made a full recovery and retained full function of his leg. However, his case has illustrated that children with NF can become unwell very quickly: NF is a surgical emergency, and senior review and definitive treatment must not be delayed.

Diagnosis of NF can be difficult and may only eventually be done at surgery. A careful history, noting the recurrence of fever after 48 hours of VZV infection and disproportionate soft tissue pain, should prompt consideration of NF and management as an emergency. Although ultrasound can be used to distinguish between NF and cellulitis, it is dependent on the availability and skill of the scanning physician and should not delay treatment or further escalation to senior staff.

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