NECROTISING SOFT TISSUE INFECTIONS AS A COMPLICATION OF CHICKENPOX

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ABSTRACT

Varicella gangrenosum, in which a necrotising soft tissue infection complicates the vesicular eruption of chickenpox, is rare. The condition may have devastating sequelae including disseminated intravascular coagulation and death. Survival is dependent on early diagnosis, adequate antibiotic coverage and, particularly, early surgical debridement. Three cases of varying severity are presented here together with a review of the available literature.

Keywords: Chickenpox, progressive bacterial synergistic gangrene

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INTRODUCTION

The typical patient with chickenpox (Varicella) goes through a brief febrile episode and then spends the next two weeks waiting for his skin eruptions to heal. Complications are uncommon - the most feared being varicella pneumonia and encephalitis. Dermal soft tissue infection is generally trivial and has little impact on the course of the illness - indeed only 4 cases have been reported in the recent literature of necrotising fasciitis complicating chickenpox and all of them were below 10 years old[1].

A recent spate of three such cases were managed at our department. The necrotising infection ranged from superficial necrotic ulcers of the penis to subcutaneous fat necrosis of the chest wall to extensive necrotising soft tissue infection of the thigh. All the cases were adults recuperating from chickenpox.

CASE REPORTS

Patient 1

The patient, a 33-year-old Chinese male heroin-smoker, had a history of thyrotoxicosis of one year's duration and was on carbimazole 10mg twice a day.

He presented on the tenth day of his varicella eruption with 2 necrotic ulcers on the prepuce of his penis and consequent phimosis.

His blood cell counts were essentially normal as were his electrolytes. He was also biochemically thyrotoxic with undetectable TSH and raised free T_4 - not unexpected given the stress of infection. Wound cultures grew *Staphylococcus aureus*, *Klebsiella* and *Escherichia coli*.

A circumcision was done under amoxil and cloxacillin cover to remove the infected and fibrotic prepuce. Histology later confirmed the presence of infection and necrosis.

Post-operative progress was excellent and he recovered completely by the fourteenth post-operative day.

Patient 2

This 24-year-old Chinese male was admitted for swelling, redness and tenderness over the sternal area, progressively worsening over one month since the fourth day of his varicella eruption. There was fever and bilateral neck and axillary lymphadenopathy but the inflamed skin over the sternum was intact. There had been no history of trauma to the chest.

Blood counts showed polymorphonuclear leukocytosis with a total white of 16000/*ul*. Red cell and platelet counts were normal. Electrolytes were unremarkable. There was a mild coagulopathy with a prolonged PTT; the PT was normal. The patient was HIV negative. Fluid and tissue cultures failed to yield any bacterial or fungal organisms. The patient was started on high doses of intravenous antibiotics viz crystalline penicillin 2 megaunits 6 hourly, cloxacillin 500mg 6 hourly, gentamicin 80mg 8 hourly and metronidazole 500mg 8 hourly.

Despite initial treatment, the patient's condition deteriorated and surgical drainage was deemed necessary on the third day of presentation.

At the time of surgery a subcutaneous collection of hemoserous fluid was found over the front of the sternum and lower part of the neck. No pus was found. A wide excision was considered inappropriate at this point and a radivac suction drain was inserted instead.

Postoperatively, although the patient felt much better, the fever was not settling, there was still an area of fluctuancy over the xiphisternum and pus began discharging from the right set of inflamed cervical nodes. He was also found to be anaemic.

A surgical debridement was thus done on the sixth day of presentation. At the time of surgery, a large anterior chest wall lesion measuring 15cm by 15cm with necrotic subcutaneous tissue was found. The underlying fascia was not involved. A wide excision was done. Histology confirmed the presence of infection but cultures were unable to isolate a causative organism. Post-operative recovery was unremarkable and when reviewed in the operating theatre one week later, granulation was well on the way.

He was finally discharged following a 16-day hospitalisation, having received a 12-day course of gentamicin and 3-week course of penicillin and metronidazole. A high protein diet was prescribed with vitamin supplements to aid healing. He declined

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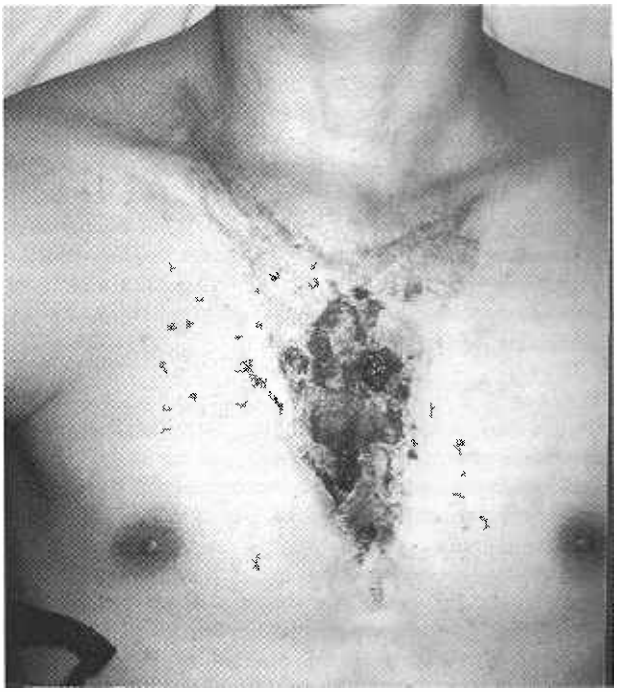
Fig 1 – The wound of patient 2 seen four months later



to have a split skin graft one month later, preferring instead to allow healing by secondary intention.

He has done very well and when last seen 4 months postoperatively, the wound had healed and contracted greatly (Fig 1).

Patient 3

This patient, a 39-year-old Chinese male drug abuser, presented with a five-day history of rapidly spreading right thigh redness and pain. This began two days into his varicella eruption. There had been no history of trauma.

He had a low grade fever and was dehydrated. His right thigh was circumferentially erythematous and indurated and large areas of necrosis and bullae had begun to form.

There were a number of biochemical abnormalities, namely polymorphonuclear leukocytosis (total white of 14200/ml) and mild thrombocytopaenia (platelets 115000/ml). His haemoglobin level was normal. Hyponatraemia (Sodium 122 mmol/l) and prerenal uraemia (Urea 23 mmol/l, Creatinine 269 mmol/l) also occurred probably secondary to dehydration.

He developed septicaemia and disseminated intravascular coagulation (PT 16.0s, PTT 61.0s) which required correction with fresh frozen plasma.

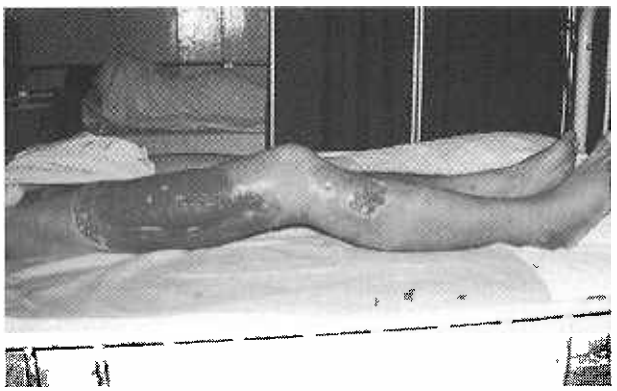
Blood cultures failed to grow any organisms. Also a HIV screen proved negative.

Urgent medical, orthopaedic and infectious disease consultation was sought. The decision was unanimous - he required surgical debridement under high-dose antibiotic cover. The antibiotic regime used was crystalline penicillin 1 megaunit 6 hourly, cloxacillin 1.5g 6 hourly and ceftriaxone 1g om.

At surgery, on the second day of admission, approximately 7% skin involvement was found on the right thigh (Fig 2). The skin came off easily from the muscle but there was no fascial necrosis. Subcutaneous necrosis was extensive. No pus was found.

Apart from anaemia that was readily corrected by transfusion, post-operative recovery was uneventful. Biochemical indices, in particular coagulation profiles, rapidly normalised. Fluid cultures grew beta-hemolytic *streptococcus, Pseudomonas aeruginosa*, Acinectobacter calco var anitratus and enterobacter

Fig 2 – The right thigh of patient 3 after desloughing showing the extent of tissue necrosis



species. The antibiotic regime was changed according to sensitivities. Histology confirmed the presence of a necrotising soft tissue infection associated with vasculitis.

Over the next three weeks the patient underwent four wound inspections and further desloughing in the operating theatre.

Finally when the wound had granulated well and was clean (as evidenced by three successive swab cultures being negative for bacteria, especially beta-hemolytic streptococci) a split skin graft was applied. By then all chickenpox vesicles had dried and fallen off and hence the donor site (the other leg) was healthy.

No problems were encountered during the split skin graft (Fig 3). Postoperatively it was important to protect against shearing forces and hence the leg was nursed in a sling lifting it off the bed. When seen again five days later in the operating theatre, there was about 60% take especially of the upper part of the thigh.

Fig 3 – Just after application of the split skin graft to the thigh of patient 3.

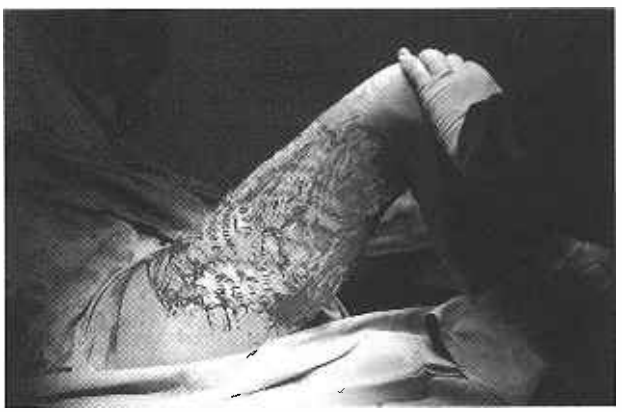
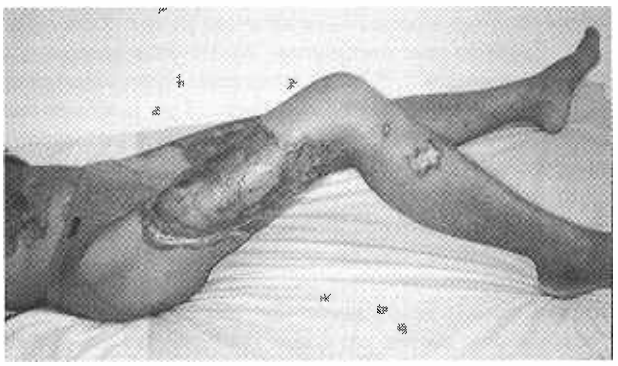


Fig 4 – The thigh of patient 3 seen two months later



He was discharged after a thirty-seven day stay in hospital. When seen two months later the wound had almost completely healed (Fig 4).

DISCUSSION

Nomenclature

There have been many attempts at classification of necrotising soft tissue infections by different authors[1]. These are generally based on the kind of pathogen, tissues involved, presence of gas in tissues, rate of progression, etc. Accordingly, Falcone et al[1] describes the general condition infective cutaneous gangrene subclassified as necrotising fasciitis and progressive bacterial synergistic gangrene (Meleny's ulcer) whereas Asfar et al[2] considers necrotising fasciitis to be synonymous with Meleny's ulcer. Hence there is much overlap among the various available classifications. Furthermore, clinical findings in different entities may also overlap[3]. Kingston et al[4] has attempted to make method out of madness by describing synergistic gangrene subclassified as rapid, moderately rapid and slowly progressive infections, adding further to the confusion. Feingold[3] has comprehensively classified gangrenous and crepitant cellulitis according to tissue involvement as summarised in Table I. Still, such classifications do serve to point out the important factors to consider when faced with such a condition, namely, (1) tissues involved (Table I) - in accordance with traditional medical terminology viz progressive bacterial synergistic gangrene (Meleny's ulcer), necrotising fasciitis, necrotising myositis, (2) rate of spread - the more rapid ones requiring early surgical exploration, and (3) bacteriology - essentially a secondary consideration as results are usually only known after initial surgical debridement and antibiotics have already been instituted. Its main value is in post-operative management and assessment of suitability for skin grafts.

The three cases presented had developed conditions resembling progressive bacterial synergistic gangrene following their varicella infections as evidenced by the extensive subcutaneous necrosis without fascial involvement. This is in contrast to necrotising fasciitis and myositis where fascia and muscle would be involved respectively and the crepitant cellulitis where tissue gas is extensive.

These classifications are, however, probably an arbitrary division of a continuum[4,5] with necrotising fasciitis and myositis at the extreme end of this continuum - hence our preference for the term necrotising soft tissue infections[6].

Bacteriology

Necrotising soft tissue infections are known to be polymicrobial[6]. Very often, even if clinical isolates contain mixtures of organisms, only single pathogens deemed causative are reported[4]. This means that broad spectrum antibiotic cover is important-cultures notwithstanding.

No specific organism or combination[2,7] of organisms has been implicated in the causation of the illness. Some of the more common organisms isolated in recent literature include Beta-hemolytic *streptococcus, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa*, Bacteroides species and Peptostreptococcus[1,2,8,9]. In fact, at one time or other almost every common bacterium has been isolated. This indicates that necrotising soft tissue infections are clinico-pathologic diagnoses independent of the specific bacteria present[8].

Predisposing factors and pathogenesis

Diabetes mellitus, obesity, alcoholism, peripheral vascular disease, immunosuppression and other factors[5,8,10] are known to predispose to severe necrotising soft tissue infections. In particular drug abusers are at high risk[8] possibly due to their general poor nutrition and attention to personal health. In our series, two patients were drug abusers while the third denied usage.

In terms of pathogenesis, it is conceivable that the varicelliform eruption acts as a portal of entry for opportunistic bacteria. From here, predisposed by the immunosuppression caused by a combination of the viraemia and the associated illness, a deep-seated infection forms not unlike the miscellaneous gangrenous cellulitis in the immunologically compromised host as described by Feingold[3] (Table I). This deep-seated inflammation can involve neighbouring vessels which undergo thrombosis. Consequently, the overlying skin undergoes infarction accounting for the finding of gangrene, bullous lesions, necrosis and haemorrhage (Fig 5).

Diagnosis

While the more superficial infections are generally easier to diagnose, deeper infections can sometimes be missed until too late. Indeed a delay in diagnosis and hence treatment is recognised as the greatest contributor to death particularly in necrotising fasciitis.

In necrotising fasciitis severe pain disproportionate[5,8] to the local physical findings is characteristic. In addition systemic toxicity (hyperthermia/hypothermia) occurs. Skin changes run the gamut from erythema, tenderness and swelling early on in the illness to cyanosis and blistering later on. An alarming finding is the progression of the skin lesion despite appropriate broad spectrum antibiotic administration. Late signs include crepitus. In fact, the two more serious cases here did present in just such a fashion indicating that all such cases should have early surgical treatment whenever possible to prevent progression especially to frank necrotising fasciitis.

Laboratory tests[5,8] are more useful in assessing associated complications than as a tool for diagnosis. Leukocytosis with shift to the left is most commonly present, but in addition anaemia, hypocalcaemia, metabolic acidosis, hypoalbuminaemia, elevated blood urea nitrogen, coagulopathies and gas on X-rays have been reported. Patient 3 also had hyponatraemia secondary to dehydration.

Recently, imaging techniques, namely MRI and CT scans, have been used to chart the progression of necrotising fasciitis[7,11]. However these changes are usually advanced and fatal by the time these methods are able to pick them up and hence a high degree of clinical awareness remains the cornerstone of diagnosis for this condition.

Treatment

By themselves, such necrotising soft tissue infections are best managed by a combination of early diagnosis, high dose antibiotic cover, and early surgical treatment. In addition, fluid resuscitation and optimal nutrition are vital[1,2,5-10].

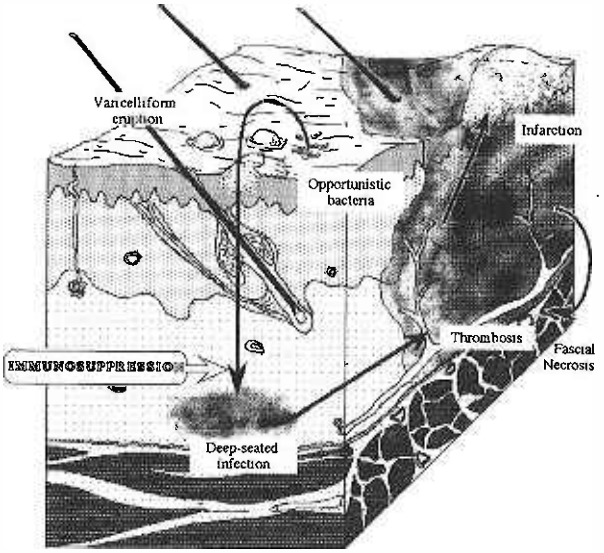
Various regimes of antibiotics have been used. We know that these infections are polymicrobial involving gram positive cocci including *S.aureus*, gram negative aerobes and anaerobes. This supports the use of a combination of high dose penicillin, an aminoglycoside and metronidazole or clindamycin in the first instance[1,8]. Alternatively, a combination of piperacillin and ampicillin has been used by Asfar et al[2] - an unusual combination given the similar spectrum of antimicrobial cover of these two drugs. However, in their series the bacteria isolated were sensitive to piperacillin with the exception of the enterococci which were sensitive to ampicillin. This combination is also relatively safe and non-nephrotoxic, prompting its use as a substitute to combinations of multiple potentially toxic antibiotics. When culture results are later known, this regime may be tailored according to sensitivities. Our preference is for the former regime

Table I - Classification of necrotising soft tissue infections

Tissue Involved	Disease	Synonyms	Characteristic Clinical Features	Progression	Predisposing Factors
Subcutaneous Tissue	Clostridial cellulitis[a]	Clostridial crepitant cellulitis, Anaerobic cellulitis	Little pain, extensive tissue gas, little skin change, foul at times	May be rapid	Local trauma
	Nonclostridial crepitant cellulitis[a]	Nonclostridial anaerobic cellulitis, Anaerobic cellulitis, Aerobic aerogenic infections, Gas abscess	As for clostridial cellulitis but usually foul	May be rapid	Diabetes mellitus
	Progressive bacterial synergistic gangrene	Bacterial synergistic gangrene, Meleny's gangrene/ulcer, Postoperative progressive gangrene	Tender, red, swollen area evolving into large ulcer with gangrenous purple margins	Moderate but relentless	Abdominal or thoracic operative wound
Fascia	Necrotising fasciitis[a]	Hemolytic streptococcal gangrene, Streptococcal necrotising fasciitis, Gangrenous or necrotising erysipelas, Perineal phlegmon, Fournier's gangrene/ syndrome	Painful, tissue gas may by present, may be foul, systemic toxicity	Rapid	Spontaneous or secondary to minor trauma, abdominal surgery or perirectal infection
Muscle	Clostridial myonecrosis[a,b]	Gas gangrene	Tissue gas present but may not be prominent, extreme toxicity which responds well to hyperbaric oxygen	Extremely rapid tissue necrosis	Local trauma, surgery or bowel pathology
	Nonclostridial myositis[a,b]	(Anaerobic) streptococcal myositis, Nonclostridial gas gangrene	No gas usually, systemic toxicity late and does not benefit from hyperbaric oxygen	May be slow	Local trauma
Any layer	Miscellaneous gangrenous cellulitis in the immunologically compromised host[a]		Similar features as all the above with variable presentations. Usually opportunistic	Variable	Immunocompromise
	Phycomycotic gangrenous cellulitis[b]	Necrotising cutaneous phycomycosis	Rare, variable presentation, no crepitus	Rapid	Diabetes mellitus, Local trauma
All Layers	Synergistic necrotising cellulitis[a,b]	Nonclostridial gas gangrene, Synergistic nonclostridial anaerobic myonecrosis, Perineal phlegmon, Fournier's gangrene/syndrome, Necrotising cutaneous myositis, Gram-negative anaerobic cutaneous gangrene	Primarily muscle involvement with secondary involvement of subcutaneous tissue and skin, dishwater pus, foul odour, Marked toxicity	Rapid	Diabetes mellitus, Perirectal infections
	Infected vascular gangrene[a,b]		Infection complicating distal gangrene seen with peripheral vascular disease	Variable	Diabetes mellitus

a Tissue gas accumulation may be detected in these entities.
b Muscle involvement is prominent in these entities.

Fig 5 – Postulated pathogenesis of varicella gangrenosum



with some exceptions as illustrated by these cases. For instance, cloxacillin was added in all three cases because of its activity against *S.aureus*. Ceftriaxone was used in place of gentamicin in case 3 as there was some evidence of renal impairment. Also, topical antimicrobials such as mafenide, silver sulfadiazine or silver nitrate have been used[1].

It has however been our experience that even in the face of such antibiotic cover necrotising infections continue their inexorable progression[8]. Clearly, the treatment of choice is surgical debridement. Radical and extensive debridement should as far as possible be performed - the price of anything less is often fatal[9]. In cases of doubtful extent, a window may be opened under local anaesthesia and odour, colour, necrosis and fascial plane status noted[8]. Depending on the extent of necrosis one may then opt for a debridement or even an amputation. Subsequent wound inspection and piecemeal debridement should then be done as often as necessary.

Reconstructive measures can be carried out later provided the donor site is healthy (a point of particular interest here as chickenpox can result in severe scarring of potential donor sites) and recipient sites are clean (as evidenced by healthy granulation tissue plus negative swab cultures done over three days).

Of special interest here is the use of antivirals (eg acyclovir and varicella immunoglobulins). It was felt that in all three cases the condition was a superadded infection rather than a fulminant viral infection (which would have evidence of multiorgan involvement namely, haemorrhagic lesions, thrombocytopaenia, varicella pneumonia, varicella encephalitis, transverse myelitis, optic neuritis, hepatitis and orchitis). As such antiviral therapy was not started.

CONCLUSION

The term varicella gangrenosum was coined to describe a complication of chickenpox in which the eruption leads to a gangrenous ulceration. This usually occurs in children with immunosuppression. It would seem now that adults are not safe either.

All cases described so far have survived as a result of prompt diagnosis, adequate antibiotic cover and, most importantly, early surgical debridement. In stark contrast to this, the mortality of necrotising soft tissue infections in general is 30-60%[6] and that of necrotising fasciitis ranges from 2% to as high as 73% in some centres[1,8]. The main contributor to higher mortality is a delay in diagnosis and appropriate treatment[8,9].

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