Streptococcal necrotising fasciitis: comparison between histological and clinical features

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SUMMARY Nineteen acute and 17 subacute cases of necrotising fasciitis due to β haemolytic streptococci are described. Excised tissue from seven and four cases, respectively, was available for histological examination. The two clinical types showed remarkable similarities, with inflammation and necrosis from epidermis to subcutaneous fat. Haemorrhage was present in variable amounts in both types. Gram positive cocci were not always identified in tissue, nor cultured, when serological tests were required to confirm the diagnosis. The only apparent difference between the acute and subacute type was the higher incidence of thrombi in some blood vessels of acute cases, whereas patent vessels or recanalised thrombus were usually found in subacute cases. This quantitative difference in the degree of thrombosis may alone be responsible for the varying clinical features and response to antibiotics.

Necrotising fasciitis due to β haemolytic streptococci (BHS) of Lancefield groups A (*Streptococcus pyogenes*), C, and G has become more prevalent, particularly in elderly or diabetic patients.¹ It usually arises as a community acquired infection, presenting clinically in an acute or subacute form,² as opposed to that following surgery for abdominal sepsis which is often due to synergy between *Bacteroides* and coliform bacteria.³ Rarely, anaerobic streptococci cause fasciitis and streptococcal "gas gangrene." We investigated patients with acute and subacute types and attempted to distinguish the relevant histological features.

Acute infection with *S. pyogenes* can be fulminating, with early septicaemic death and disseminated intravascular coagulation, when only a small amount of localised necrotic tissue need be present.⁴⁻⁶ Alternatively, rapidly spreading tissue necrosis can occur after a trivial or inapparent injury, which usually follows the venous drainage above the fascial layer. This is called acute "necrotising fasciitis," although it is really a "necrotising supra-fasciitis." This can also proceed to septicaemia and rapid death and must be managed surgically, as originally described by Meleney.⁷ It has been caused by BHS groups A, C, and G.^{2,7-9}

Spreading tissue inflammation can initially look

like erysipelas or cellulitis. This may proceed to localised blistering, ulceration, and necrosis, but these patients have nearly always received antibiotics before this occurs. When the infections fails to resolve completely with antibiotics, necrosis of tissue overlying the fascial planes slowly develops, with the formation of a thick eschar that can take weeks or months to slough off. This is called subacute "necrotising fasciitis." These patients should also be managed surgically, but they rarely die.^{2,8} This type has previously been called "ulceration following cellulitis"² and is caused by BHS groups A and G. To make the diagnosis reliance was placed on serial antibody tests to streptolysin O, deoxyribonuclease B, and hyaluronidase (groups A and C/G), as described previously.⁸ This is because the open blistering lesions may not contain the streptococcus and are often contaminated with other bacteria.

Patients and methods

We have seen 21 patients with necrotising fasciitis in Southampton and 15 in Harrow over the past five years (tables 1 and 2). The histology of tissue excised from 11 of these patients was reviewed.

HISTOLOGY

Tissue was collected into formalin. Selected blocks were processed for routine paraffin embedding, and

3 µm sections were cut and stained using haematoxylin and eosin and Gram stains.

Post mortem examinations were carried out on two patients who died of the acute infection, but tissue was not available from one necropsy that had been performed by the coroner's pathologist. Tissue retained for study from the other case included skin and subcutaneous tissue collected from the site of infection as well as heart, lung, spleen, kidney, liver, pancreas, parathyroid, coronary artery and bone, but not brain.

BACTERIOLOGY

Swabs from superficial blisters and purulent discharges were plated out on to blood agar and incubated aerobically and anaerobically at 37°C. They were also inoculated into Todd-Hewitt broth. Excised tissue was ground up inside a safety cabinet and was both placed out on blood agar and inoculated into Todd-Hewitt broth containing β lactamase, as tissue has been found to contain a variable amount of penicillin. This had been noticed on culture plates when streptococcal colonies only grew up away from the main pool of the inoculum of "ground up" tissue.

Subcultures of the broth were made, both aerobically and anaerobically, after incubation for one week at 37°C. Selective agar for isolating streptococci and staphylococci, such as crystal violet or nalidixic acid and colistin (Oxoid SR70), were not found to be necessary for all specimens but were used if secondary infection of open wounds had occurred. Streptococcal colonies were identified by haemolysis and growth on bile-aesculin and blood agar and were grouped by a coagglutination method (Phadebact or Streptex): isolates were kindly M typed by Dr G Colman at the Division of Hospital Infection, Central Public Health Laboratory, Colindale. *Staphylococcus aureus* was identified by the tube coagulase test and other bacteria by standard laboratory techniques. Serial samples of serum were examined from patients with subacute necrotising fasciitis for antibodies to streptolysin O, deoxyribonuclease B, and hyaluronidases.⁸

Results

Tables 1 and 2 show the results, together with patient details; table 3 gives the histology results.

Table 1 Cases of acute necrotising fasciitis

Case No	Age	Sex	Coexisting illness	Site of lesion	Bacterial culture	Outcome
<i>Cases of acute necrotising fasciitis due to BHS:</i>						
1	77	F	None	Left elbow	GpA BHS, M64 —blood cultures/elbow	Died, septicaemic
2	72	M	Paraplegia due to poliomyelitis	Left ankle	GpA BHS, M22 —blood cultures/ankle	Died, septicaemic
3	35	M	None	Right eyelid/face	GpA BHS, M73 —blood cultures	Died, septicaemic
4	70	F	COAD	Right leg	GpG BHS	Died, toxæmic
5	56	M	None	Right hand/arm	GpA BHS, M1 —blister fluid/necrotic tissue	Debrided and grafted
6	43	M	None	Right thumb/arm	GpA BHS, M3*	Debrided and grafted
7	30	M	Diabetes	Right leg	GpA BHS, M— and <i>S aureus</i>	Debrided
8	45	M	Diabetes	Right eyelid	GpA BHS	Debrided late and grafted
9	72	F	None	Left eyelid	GpA BHS, M75	Debrided late and grafted
10	70	F	None	Right index finger	GpA BHS, M1	Amputation
11	61	F	None	Left index finger	GpA BHS	Amputation
12	75	F	Obese	Right leg	GpA BHS	Debrided; died after anaesthetic CVA
13	54	F	None	Right thumb	GpA BHS, M1	Debrided
14	82	F	Atherosclerosis	Left leg	GpC BHS	Debrided and grafted
15	75	F	Syringomyelia	Left leg	GpG BHS	Debrided
16	80	F	None	Right leg	GpG BHS	Debrided and grafted
<i>Case of acute necrotising fasciitis and myositis due to anaerobic streptococci:</i>						
17	65	F	Diabetes	Left toe/foot	Anaerobic streptococci	Amputation

*BHS GpA + *S aureus* isolated at site of injury in thumb, but pure BHS GpA isolated from spreading lesion up arm.

M— = M non-typable.

Table 2 Cases of subacute necrotising fasciitis due to BHS

Case No	Age	Sex	Coexisting illness	Site of lesion	Bacterial culture	Haematological serological result	Outcome
1	69	M	None	Left knee	GpA BHS		Debrided
2	73	M	None	Right foot	GpA BHS, M2	A	Eschar sloughed after 5 months
3	72	F	Diabetes	Left thumb	GpA BHS, M64	A	Healed with penicillin
4	74	M	None	Left leg	GpA BHS, M— (blisters/blood culture)		Healed with penicillin
5	77	M	Atherosclerosis	Right foot	No growth	A	Debrided
6	72	F	None	Right leg	<i>S aureus</i>	A	Debrided
7	68	F	None	Right foot	<i>S faecalis</i> and <i>Proteus</i> sp	A	Debrided
8	41	M	None	Left elbow	No growth	A	Incised and drained
9	22	F	None	Right leg	GpA BHS and <i>S aureus</i>	A	Debrided
10	49	F	None	Left ankle	GpG BHS	A	Debrided
11	73	F	None	Right elbow	GpA BHS, M49		Healed with penicillin
12	75	F	Right hallux	Right foot valgus	GpC BHS		Healed with penicillin
13	75	M	None	Right leg	GpG BHS		Debrided
14	83	F	Wound sinus	Right leg	No growth	C/G	Healed with penicillin
15	82	M	None	Right thigh	<i>S aureus</i>	A	Debrided
16	63	M	None	Right thigh	<i>S aureus</i>	A	Debrided
17	65	F	Systemic lupus erythematosus on prednisone	Buttock	<i>S aureus</i> and <i>Bacteroides</i> sp	A	Debrided
18	77	F	None	Right leg	No growth	A	Penicillin V; healed in 1 month
19	63	F	None	Right arm	No growth	A	Debrided

ACUTE NECROTISING FASCIITIS (TABLE 1)

Three patients had septicaemia with growth of BHS group A in blood cultures, all of whom died. Case 1 developed the infection around the elbow while in hospital. Case 2 was admitted to hospital with necrosis around the ankle and died within 48 hours. Post-mortem examination showed that there was ante-mortem thrombus present in the subcutaneous tissue of the ankle, capillaries, and a small artery of the lung; in a vein and small artery of the heart (fig 1); and in a small artery of the spleen. Thrombus was not found in sections of liver, kidney, and pancreas, and there was no evidence of a streptococcal myositis in heart muscle. Case 3 developed erythema and oedema of the right upper eyelid spreading upwards over the forehead and scalp and downwards over the cheek, neck, and upper chest three days after his daughter poked him in the eye. Frank pus was found discharging from the conjunctiva from which Gram positive cocci were seen but failed to grow on culture. Before surgery could be undertaken he had a cardiopulmonary arrest from which spontaneous respiration never recurred.

Biopsy specimens were taken within five days after the infection had occurred. Localised areas of oedema and necrosis were found in both the dermis and epidermis; some areas showed large numbers of polymorphonuclear leucocytes invading this necrotic

Fig 1 Thrombus in small artery of heart in disseminated intravascular coagulation due to *S pyogenes* septicaemia (Haematoxylin and eosin.) $\times 157.5$.

Table 3 *Histological features of streptococcal necrotising fasciitis (gangrene)*

Case No	Epidermis	Dermis			Blood vessels		Bacteria
		Superficial	Deep	Subcutaneous fat	Lumen	Wall	
Acute cases							
2	Absent	← Confluent necrosis →			Occasional thrombus	Intimal thickening	Numerous Gram positive cocci in necrotic dermis
3	Focal necrosis	← Oedema and severe inflammation (mainly neutrophils) →			Patent	Normal	Gram positive cocci in neutrophils and hair follicles
5	Inflamed or necrotic and lifting off	Confluent necrosis or haemorrhage and inflammation	Mild inflammation	Necrosis and severe inflammation (mainly neutrophils)	Occasional thrombus	Normal	Not seen
7	Inflamed or necrotic and lifting off	Confluent necrosis or haemorrhage and inflammation	← Confluent necrosis or inflammation (mainly neutrophils) →		Thrombus in inflamed or necrotic areas	Intimal thickening	Numerous Gram positive cocci in inflamed or necrotic areas
10		← Haemorrhage, inflammation and necrosis (mononuclear cells, neutrophils) →			Occasional thrombus	Intimal thickening	Not seen
14	Confluent necrosis	← Inflammation and confluent necrosis (mainly neutrophils) →			Occasional thrombus	Intimal thickening and arteriosclerosis	Not seen
15		← Inflammation and confluent necrosis (mainly neutrophils) →		Inflammation, necrosis and haemorrhage (mainly neutrophils)	Occasional thrombus	Normal	Not seen
Subacute cases							
1	Necrotic or absent	← Necrosis and severe inflammation (mainly neutrophils) →			Patent	Arteritis in inflamed areas	Numerous Gram positive cocci in fat
5		← Haemorrhage and necrosis →			Occasional recanalised thrombus	Severe intimal thickening and arteriosclerosis	Not seen
6	Intact	Mild inflammation	← Necrosis, haemorrhage and severe inflammation (mononuclear cells, neutrophils) →		Patent	Intimal thickening	Not seen
18	Necrotic or absent	← Focal necrosis and inflammation (mainly neutrophils) →			Patent	Normal	Numerous Gram positive cocci

tissue (fig 2). Inflammation was severe in the subcutaneous fat, which became necrotic. The excised material extended to, but not through, the fascial layer, which would have appeared healthy at the time of surgery. Pre-excision thrombus of some vessels was present in all but one specimen, and at times was surrounded by very large numbers of Gram positive cocci (fig 3), whereas other vessels were patent. Endarteritis or arteriosclerosis and calcification of vessels was present in some patients. Haemorrhage into the tissue was found in two of seven patients.

Case 17 developed "gas gangrene" of the foot from which a pure growth of anaerobic streptococcus was isolated without other bacteria being present. Serial serology showed no evidence of infection by either BHS or *S aureus*. She was diabetic and had suffered an

interdigital foot ulcer for two weeks before hospital admission, having been treated with amoxycillin by her local doctor. Gas was present in tissues which were fully debrided on admission, when very large doses of benzyl penicillin and metronidazole were given, but the necrotising infection continued to spread through the plantar tissues of the foot so that amputation became necessary. Histology showed acute inflammation with patchy necrosis of muscle and fat. Degenerative arterial disease was present but not to an extent that could be responsible for the necrosis.

SUBACUTE NECROTISING FASCIITIS (TABLE 2)
Biopsy specimens were taken 12 to 16 days after the infection had occurred, when all the patients had been treated with antibiotics. The epidermis varied between

Fig 2 *Oedema and impending necrosis of epidermis and dermis in acute streptococcal gangrene showing thrombosed blood vessels and large numbers of polymorphonuclear cells (Haematoxylin and eosin.) $\times 65$.*

Fig 3 *Large numbers of Gram positive cocci surrounding thrombosed vessels in acute streptococcal gangrene (Gram stain.) $\times 195$.*

Fig 4a *Thrombosed vessel in case of subacute streptococcal gangrene, surrounded by polymorphonuclear cells (Haematoxylin and eosin.) $\times 157.5$.*

Fig 4b *Recanalised vessel in case of subacute streptococcal gangrene (Haematoxylin and eosin.) $\times 157.5$.*

being healthy, acanthotic, or necrotic, but extensive inflammation was present in the lower dermis and subcutaneous fat. The presence of thrombus, Gram positive cocci, and tissue haemorrhage was variable. In one patient (case 5) there was full thickness necrosis of the dermis and much haemorrhage present in the tissues, but organisms were not seen; both thrombosed and recanalised vessels were present (figs 4a and b). The differential diagnosis from an embolus was confirmed by finding rising antibody titres to streptolysin O, deoxyribonuclease B, and hyaluronidase.

Discussion

Haemolytic streptococcal infection of soft tissues can cause cellulitis or rapidly spreading necrosis or it can be a source of septicaemia and death. In our hospitals BHS group A was isolated from blood cultures from three patients after their death, having been collected before death in the preceding 48 hours. In the first patient (case 1, table 1), a similar BHS group A (M type 64) to that causing septicaemia was isolated from soft tissue, showing early necrosis that surrounded the elbow. It was also isolated from other patients, including case 3 (table 2), and staff in a hospital ward outbreak.² In the second patient (case 2) a similar BHS group A (M type 22) to that causing septicaemia was isolated from early necrosis around the ankle and also from the throat of a close relative who directly cared for him. The third patient who died had been "poked" in the eye by his daughter, who developed an area of impetigo on her face three days after her father's illness began and from which BHS group A was isolated. This infection needs to be recognised early when there is severe toxemia. Post mortem histology has shown evidence of disseminated intravascular coagulation (DIC), which can be expected to contribute to the ensuing rapid death. Heparin was given intravenously by Graybill *et al.*,¹⁰ together with antibiotics, and by Hammar and Wanger,¹¹ in doses guided by activated partial thromboplastin time studies at an early stage, when they successfully treated two of eight patients with necrotising fasciitis. Haemorrhage, however, occurred in the necrotic tissues of our patients, without heparin being given, and this possibility must be considered, even though the beneficial effect of controlling the DIC over the critical septicaemic period may well be greater and permit better tissue perfusion with penicillin at sites close to the necrotic lesion.

We continued to grow BHS group A from necrotic discharging tissue five days after starting benzyl penicillin at 20 U/day because of the failure of penicillin to penetrate through thrombosed vessels. It is thus essential to debride the infected necrotic tissue at an early stage to prevent the infection from spreading or recur-

ring when antibiotics are stopped. Gangrenous tissue excised from patients infected by BHS groups C and G^{9 12} contained penicillin so that the degree of thrombosis caused by these strains was less than that of BHS group A. We found that granulation tissue formed rapidly after debridement, after which skin grafting was usually satisfactory. If the necrotic tissue is allowed to slough off medically it can take months to do so and be a source of reinfection. This applies particularly to subacute necrotising fasciitis where we have found severe inflammation in the dermis and subcutaneous fat with, on one occasion, recanalised thrombosed vessels. Retrograde venous flow or a collateral circulation may be mechanisms underlying the haemorrhage sometimes seen in the tissue, but ultimately necrosis occurs where there is an insufficient blood supply. In this situation cultures may be negative or misleading; better confirmation is gained by serial serological tests.⁸

The infections described by ourselves and Meleney⁷ did not spread into muscle, although they can occasionally spread between muscle bundles beneath the fascia: amputation was not generally required and debridement to the fascial layer was sufficient. Amputation of an index finger, however, was required in two patients (cases 10 and 11, table 1) where the blood vessels were extensively thrombosed. This type of infection differs from acute streptococcal rhabdomyolysis, where there is an overwhelming infection of skeletal muscle in different sites, and has so far always been fatal (Gilks CF, Lambert HP, Lansborough Jones M, personal communication).^{13 14} It is thought to occur when there is a simultaneous picornavirus infection, causing a viral myositis and a streptococcal bacteraemia.¹⁵ BHS group A only infects skeletal muscle directly when inoculated in association with anaerobic streptococci in serious wounds when its distinction from clostridial gas gangrene must be considered.^{16 17} Anaerobic streptococci alone, however, can infect muscle as a rare event in immunocompromised patients or diabetics (case 17, table 1), when the clinical presentation is of "gas gangrene"; anaerobic streptococci are prolific producers of hydrogen sulphide gas from muscle. A spreading necrotic process occurred in this patient that could only be halted by amputation through the ankle. As anaerobic streptococci can be difficult to grow and need to be incubated under strict anaerobic conditions for at least one week at 37°C, they may be missed as a cause of the acutely infected diabetic foot.

Necrotising fasciitis due to BHS occurs when the organisms spread through tissue above the fascial plane, causing a thrombosis of vessels that results in gangrene of the dermis and subcutaneous fat. Meleney reported the pathological effects of streptococcal gangrene in detail in 1929 and 1933,^{7 18} when surgery

was the only form of treatment, and commented that both venules and arterioles were often found filled with thrombi but that patent blood vessels could also be present in the extensive slough supplying islands of relatively normal skin. He also noted that the infection never affected muscle or bone deep to the fascia unless injury exposed these structures. Webb *et al*¹⁹ commented similarly, but contrasted the histology with that of erysipelas where streptococci are found in the epidermis causing a polymorphonuclear cell infiltrate with cellular oedema and dilated blood vessels and lymphatics; lymphangitis was rarely found in necrotising fasciitis which has also been our experience. Others^{11 20 21} have noted extensive subcutaneous necrosis and collagen fragmentation with large numbers of streptococci and polymorphonuclear leucocytes in the spreading margin of the lesion. They also found that streptococci were usually absent from more superficial tissues and that skin in the area of "blue patches" was necrotic but nearby skin could be only congested. These effects result in the variable clinical features of patchy dusky discolouration of skin and blistering alongside normal and gangrenous skin with no clear distinguishing margin between them. The histological features are also variable but depend as well on the site and depth of tissue biopsied. Common features for both the acute and subacute types include severe inflammation of the dermis and subcutaneous fat with patchy necrosis and tissue haemorrhage. While occasional thrombus was usually found in vessels from the acute type, biopsied within five days, vessels in the subacute type were patent or recanalised—but had been biopsied one week later. The lesion is best studied with multiple sections taken from the spreading edge right through the necrotic tissue. Whether streptococci can be found depends on the site biopsied and the stage of the infection; in late stages evidence of streptococcal infection may only be available from specific serology.

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