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ORIGINAL STUDY

Diagnostic pitfalls in the differentiation between pyoderma gangrenosum and necrotizing fasciitis

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Pyoderma gangrenosum and necrotizing fasciitis are two rare pathologic entities with a similar clinical image, but a who require a very different management. In general physicians, orthopedics, dermatologists, plastic surgeons will hardly ever see it, but when they do it is very important to distinguish between both. In this paper with the focus on the practical approach ,we expose the diagnostic pitfalls in the differential diagnosis, explain how to prevent them and summarize the evidence on therapeutic management. To achieve this we use a case where the diagnosis was rather difficult and utilize reviews where the clinical features, early diagnostic tools and treatment options are explained.

Keywords : necrotizing fasciitis; pyoderma gangrenosum.

INTRODUCTION

Necrotizing fasciitis (NF) is a rapidly spreading soft-tissue infection first described by Hippocrates in the 5th century BCE which typically follows an injury to the involved site. Toxin producing virulent bacteria like group A beta-hemolytic streptococci (NF type 2) are often the causative agent. Multibacterial (NF type 1) and Marine Vibrio species (NF type 3) are also described. The infection usually presents at the extremities, but NF can affect any body part. The incidence proportion is 4 cases per 10^6 persons per year. Despite more effective and faster therapeutic treatment the last couple of years the mortality of this life-threatening infection is still 9.3% *(3)*. Pyoderma gangrenosum (PG), first described in 1908 by Brocq, is a primarily sterile inflammatory neutrophilic dermatosis. Due to the possible similar clinical image it can be easily misplaced by NF. Although the etiology of PG is unknown, a number of familial PG cases have been reported, suggesting that genetic factors might be involved in the pathomechanism of PG. For example PG occurs by the association of a JAK2 mutation that activates the JAK-STAT pathway, a common mechanism involved in the pathogenesis of inflammatory and hematologic diseases. Another example are mutations in the PSTPIP1 gene, typically present in patients with PAPA syndrome, a rare auto inflammatory disorder including pyogenic sterile arthritis and acne with autosomal dominant inheritance *(11,12)*. The peak of incidence occurs between 20 to 50 years with women being more affected then men. The general incidence has been estimated to be between 3 and 10 per 10^6

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per year. It affects usually the trunk and the lower extremities, but also here other body parts can be involved *(13,17)*. Powell et al. *(14)* classified PG into 4 major clinical types (Table I).

Table I. — The different clinical types of PG

Clinical variants	Typical findings
Ulcerative PG	Ulceration with rapidly evolving purulent wound ground
Pustular PG	Discrete pustules, sometimes self-limited, commonly associated with inflammatory bowel disease
Bullous PG	Superficial bullae with development of ulcerations
Vegetative PG	Erosions and superficial ulcers

PATIENTS AND METHODS

A 48-year old men presented at the emergency department with fever (39,1°C) and pain localized at his left hand and forearm. Two weeks prior to this he sutained a multifragmentary diaphyseal midshaft humeral fracture at the same side after a fall. A Sarmiento brace was applied in order to obtain a healing by conservative means . By clinical examination the hand and forearm were swollen. No penetration or pressure wound could be found as possible agent for infection. The Sarmiento brace was loosened, but the swelling persisted. A deep venous thrombosis could be excluded by a negative duplex scan. Laboratory findings showed a C-reactive protein (CRP) of 328 mg/dl, a hemoglobin level of 12,0 g/dl, a white blood cell count of 16700/µl with left shift, an INR of 1,09, a creatinine level of 0,75mg/dl, and an LDH of 701U/l. Urine cultures, blood cultures and a thoracic X-ray taken during fever episode at the emergency department showed no peculiarities. A hospital stay was advocated . 24 hours later an increase in pain and a bullous formation with augmentation of swelling was noticed. A puncture was done and the fluid sent for culture. A medication scheme of diclofenac 75mg intramuscular (IM), paracetamol 4x1g intravenous (IV), and flucloxacillin 6x1g IV in a 20cc sodium chloride solution was applied. The fever disappeared and new blood cultures were taken. The day after all samples showed negative results. Repeat cultures remaid negative. The patient's medical history illustrated besides a meningitis in childhood an important treatment for a presumed NF at chest level 14 years earlier. A removal of a considerable part of the pectoralis muscle was necessary and a skin graft was applied. In consideration with the patient his family he was transferred to the hospital where he was treated 14 years ago. Remarkably the patient's brother had been treated at that hospital for similar symptoms. However, his final diagnosis was not a NF but rather a PG. By arrival an antibiotic scheme of clindamycin 3x600mg IV and cefepim 3x2g IV and rehydration therapy (1l sodium chloride 0.9% per 12h) was applied. Supportive analgesic therapy contained paracetamol 4x1g IV and tramadol 3x100mg/ml orally. That night an urgent contrast MRI of the left forearm was taken showing evidence of NF. According that result a surgical release, decompression and debridement of the left arm was performed. The next day there was already an enlargement of the lesions and a revision was necessary. During surgical revision however the clinical aspect of a part of the wound could fit by PG. High dose steroids (IV 120mg methylprednisolone) were adjusted. From a pathologic point of view the histologic correlate fitted more the diagnosis of a NF at the first operation and of PG at the revision . Because of the suggestive clinical appearance ,the steroid treatment was continued together with the latter described medication scheme. From then on the situation remained stable enough to apply a vacuum assisted closure (VAC) to stimulate granulation of the wound. One week later the patient was stable enough to leave the intensive care unit. Antibiotics were stopped and steroids were further downgraded. Another week later split-thickness autografts at the left thigh region were preleased and applied. Postoperatively the graft showed a favorable growth into the original tissue. During the next visits the grafted zone further evolved in a positive way and the donor site was almost fully cured. The left arm was progressively mobilized with the professional help of a physiotherapist and adequate wound management remained. During and also after his stay the patient could always count on professional psychologic support.

DISCUSSION

Background

NF is mainly a clinical diagnosis. In the medical history 31,4% of the cases have a former trauma of which 4,3 % is caused by surgical wounds. Diabetes mellitus is the most common co morbidity involving 44,5% of patients. Other co morbidities who also result in an immunocompromised status like obesity, peripheral vascular diseases, intravenous drug abuse, alcohol abuse, malnutrition, smoking, chronic cardiac disease, chronic immune suppression, steroid therapy, cancer and age are also risk factors for NF. Although numerous risk factors have been identified half of all cases of NF occur in previously healthy individuals *(3)*. The triad of pain (79,0%), swelling (80,8%) and erythema (70,7%) which also could be observed in our patient is very characteristic. Other features are showed in Table II *(9)*. Initially the pain is inordinate with the present swelling and erythema.

Table II. — Typical features of NF

Number of patients	1463
Symptoms (%)	
Erythema	70,7
Warmth	44.0
Pain	79.0
Swelling	80.8
Bullae	25.6
Crepitus	20.3
Skin necrosis	24.1
Fever >37,5°C	40.0
Hypotension	21.1
Gas on X-ray (%)	24.8
Microbiology (%)	
Positive wound culture	76.5
Monomicrobial	46.5

The increase in skin sensibility is typically due enzymes and toxins spreading through the fascia beneath the skin. The affected wound margins are irregular and histopathological lymphangitis of the skin itself is hardly present because of the deep presenting infection. Further presenting features are a grey necrotic suppurating edematous fascia, thrombotic veins, a thin watery foul-smelling fluid described as dishwater pus, non-contractile muscles and minimal changes in the dermis of the skin. In our patient deep abscess forming and a necrotizing process over the full length of the skin was apparent. Thrombotic formation was not present. Despite antibiotic use NF will evolve very quickly. The best way to diagnose NF macroscopically is by applying the 'finger test'. Under local anesthesia a 2 cm incision is made down to the deep fascia and a gloved finger is inserted to its base. The index finger dissecting the subcutaneous tissue easily from the fascia defines a positive test. Together with histopathologic findings direct inspection from the fascia during surgery remains the golden standard in diagnosing NF *(9)*.

The following described diagnostic tools could help to support the diagnosis, but never should delay medical intervention and therapy. Microbiologically Wong et al. *(19)* created a score (Laboratory Risk Indicator for Necrotizing Fasciitis or LRINEC) to discriminate between NF and non necrotizing soft-tissue infection (Table III). A total score of 6 as in our case predicts a probability between 50 and 75%.

Table III. — LRINEC
(Laboratory Risk Indicator for Necrotizing Fasciitis) (1)

Value	Score	Our case
C-reactive protein (mg/l)		328
<150	0	
>150	4	
White blood cell count (cells/µl)		16700
<15000	0	
15000-25000	1	
> 25000	2	
Hemoglobin level (g/dL)		12.0
>13.5	0	
11-13.5	1	
<11	2	
Sodium level (mmol/L)		138
>/= 135	0	
<135	2	
Creatinine level (mg/dL)		0.75
</= 1.6	0	
> 1.6	2	
Glucose level (mg/dL)		100
</=180	0	
>180	1	
	Total: 6	

The serum creatinine phosphokinase level (CPK) in the early diagnosis can help to distinguish the type of NF more specifically. Significant highly elevated CPK values direct towards a group A beta-hemolytic streptococci infection (NF type 2, or the so called flesh-eating bacteria) *(15)*. In our patient a CPK value of 54U/l made the diagnosis of NF type 2 unlikely. In 24.8% of all cases gas in soft tissue could be detected by plain radiographs. CT scans are sensitive in identifying soft tissue edema and are more useful in evaluating the margins of infection. Fascial fluid detected on T2-weighted MRI images have a sensitivity between 93 and 100 % in diagnosing NF. This fascial fluid together with edematous formation of the subcutis and the surrounding muscle tissue was clearly visualized in our patient. Besides several abscess collections could be found. Frozen-section biopsies can, when the diagnosis is unclear and the patient is stable, also be used for diagnostic work up.

60% of the PG cases are associated with underlying systemic diseases like inflammatory bowel disease, rheumatological or hematological disorders and malignancies. In 1930 this link was already described by Brunsting et al. *(5)* although they thought that PG could be explained by a streptococci or staphylococci infection in an immune suppressed patient. Secondary infection or invasion by commensal bacteria is possible though and can harden the diagnostic work up. In 1985 Fulbright et al. *(8)* formulated the now generally accepted hypothesis where PG is seen as an aberrant immune response on still to be identified contributing factors. A cross-reaction with underlying disease where the pathways protecting the epidermis from the neutrophilic infiltration are insufficiently working, would form the cutaneous manifestation *(17)*. Because of the latter it is important to take the medical history into the diagnostic process. In our case there wasn't a known systemic disease. Moreover there should be noticed that these associated diseases could also align ulcers due to other disease conditions *(18)*. Pathergy occurs in 25-50% of cases, where dermatologic lesions develop at the site of minor trauma. Surgical debridement is therefore contraindicated as it would aggravate and accelerate the disease process *(7)*. In our case initially there wasn't a pathergy phenomenon detected. Although afterwards one may question the precise reason why revision was necessary. Typical clinical features of PG are recurrent cutaneous ulcers with mucopurulent or hemorrhagic exudate. The wound margins are regular and violaceous. Su WP et al. *(16)* proposed two major and four minor criteria, strictly to be used in a clinical setting to diagnose an ulcerative type of PG. A positive diagnosis requires both major criteria and at least two minor criteria (Table IV). One may notice that in this classification they assume an irregular wound margin as a key criterion. Contrary to NF there are no diagnostic laboratory criteria or typical histopathologic findings. This makes PG more a diagnosis of exclusion. Table V presented by Mahajan AL et al. *(10)* shows both entities in a clarifying summary

Table IV. — Criteria of classic, ulcerative PG

Major criteria 1. Rapid progression of a painful necrolytic cutaneous ulcer with an irregular, violaceous and undermined border 2. Other causes of cutaneous ulceration have been excluded
Minor criteria 1. History suggestive of pathergy or clinical finding of cribriform scarring 2. Systemic disease associated with PG 3. Histopathologic findings (sterile dermal neutrophilia +/- mixed inflammation +/- lymphocytic vasculitis) 4. Treatment response (rapid response to systemic steroid treatment)

Approach and treatment

There are five important pillars of therapy for NF: early diagnosis and aggressive debridement, broad-spectrum antibiotics, aggressive resuscitation, frequent re-evaluation and comprehensive nutritional support. Surgical debridement is the cornerstone of management because it is the fastest and most effective way to reduce the bacterial load and halt the necrotic process. This is the only intervention proven to increase the rate of survival. Hereby it is of great importance to remove all necrotic tissue even if this leads to a necessary amputation. Daily careful management of the extensive wounds is critical and these should be

Table V. — Table comparing features of PG and NF

Features	Pyoderma gangrenosum	Necrotizing fasciitis
Pain	Superficial	Deep
Associated systemic disease (IBD°, arthritis,…)	Yes (60%)	No
Early lesions	Pustule/nodule	Cellulitic-like
Established lesions	Well defined violaceous ulcer edge	Poorly defined border
Multiple lesions	Yes	No
Satellite lesions	Yes	No
Pathergy	Yes (20-40%)	No
Disease progression	Progresses gradually over days	Progresses within hours
Hemodynamic instability	No	Yes
Positive cultures	No	Yes
Inflammatory infiltrate	Predominantly neutrophilic	Mixed infiltrate including neutrophils
Vessel thrombosis	Yes	Yes
Necrosis	Yes	Yes
Response to steroids	Yes	No
Response to surgery and antibiotics	No	Yes

° IBD: Inflammatory bowel disease

kept covered to protect against secondary infection, encourage the formation of granulation tissue and absorb inflammatory exudates. Both alginate and hydrogel dressings with or without negative pressure have been used successfully. Once the infection has resolved and a bed of healthy granulation tissue is present, the wound may be closed with skin flaps or split-thickness grafts. One week after debridement this procedure was also done in our case. Antibiotic therapy cannot be the sole treatment because fascia is poorly vascularized and the disease process further reduces its blood supply. Despite having little effect on the wound itself, its value lies in the power to reduce the bacterial load and termination of toxin production. It also protects against organ failure. In table VI the widely accepted antibiotic scheme is presented. Besides antibiotics and surgical debridement an adequate fluid resuscitation, nutritional support and blood pressure support are essential. Furthermore one may underline the huge importance of an adequate analgesic therapy. Adjunctive therapies include intravenous immunoglobulin G (IVIG) to inhibit the activation of T-cells and cytokine production, the use of hyperbaric oxygen (HBO) and recombinant human-activated protein C for sepsis therapy *(3)*. The best documented treatments for PG are systemic corticosteroids and cyclosporine. According Brooklyn et al. *(4)* an urgent referral to the dermatology department is needed once suspect signs are presenting. Oral corticosteroids (with or without minocycline) are recommended as first line treatment. If patients do not respond promptly, infliximab is used as this has fewer recognized side effects than cyclosporine and has been used widely in inflammatory bowel disease and rheumatoid arthritis. An induction dose regimen of 5mg/kg at weeks 0, 2 and 6, followed by further treatments as necessary, depending on response are recommended. Azathioprine, another immunosuppressant should be given at the same time as infliximab. While this approach is not strictly evidence based, it is now accepted practice in other inflammatory conditions, such as Crohn disease. So the main therapeutic treatment of PG beholds several factors. First of all one should be aware of associated diseases if there are. Generally the treatment then consists out of two parts: local and systemic. Local therapeutic options include debridement, dressings of hydrocolloid type and/or

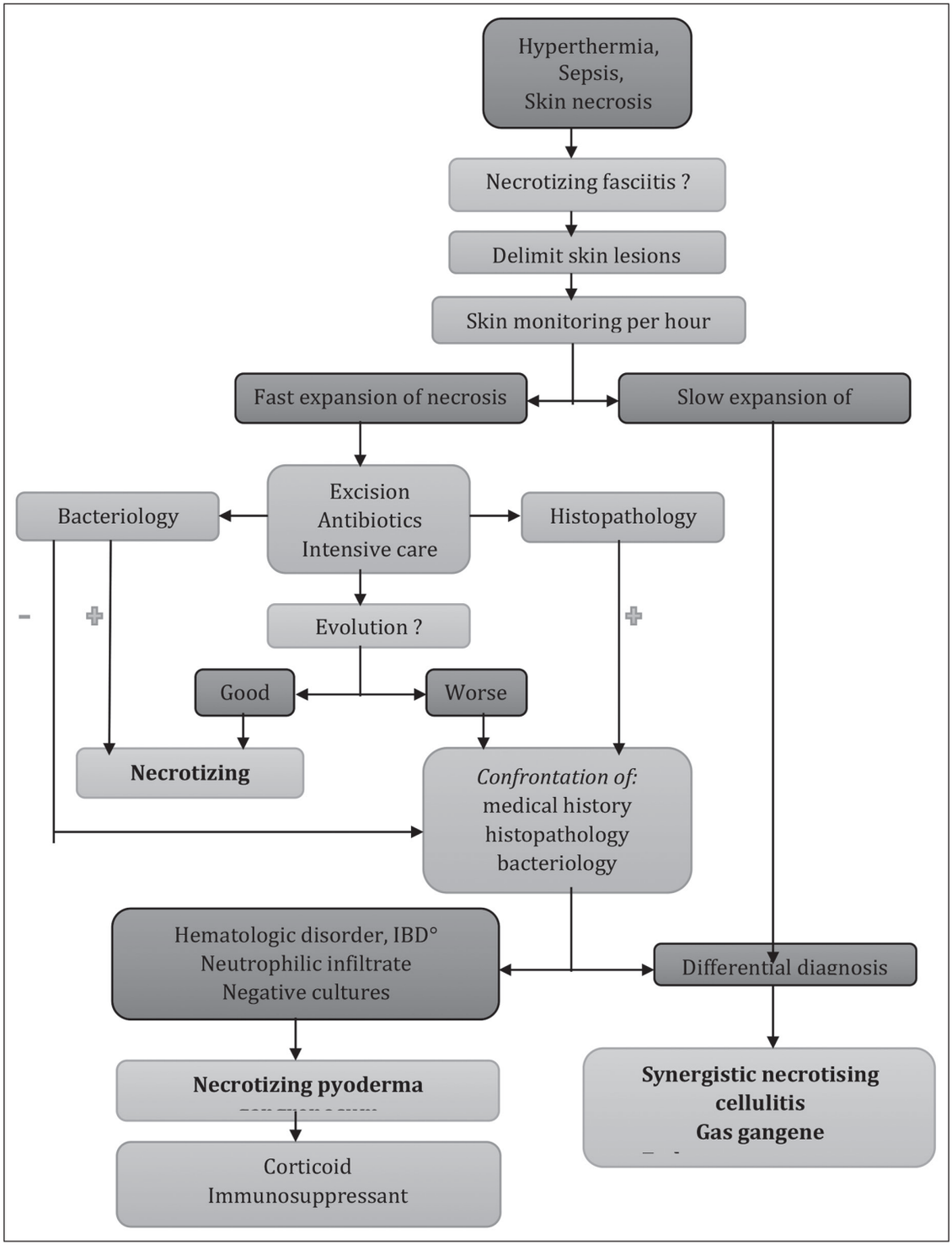

Fig 1. – Algorithm according Ayestaray et al. This algorithm is a help for the surgical course, but cannot replace the medical discussion for each clinical situation. although immunosuppressive treatment may worsen the evolution of a NF to start with corticosteroids in association with antibiotics. As clinical and biological improvement is noticed after starting corticosteroids and histological results make a NF unlikely the antibiotics could be stopped.

allograft installation to support re-epithelialization, topical agents and intralesional injection of steroids or cyclosporine. Systemic therapy typically comprises oral prednisone (40-120mg/d). It is administered in high doses until lesional clearance is obtained. Subsequently, a low maintenance dose is used to maintain remission *(6)*. A quick intervention is anyhow of primordial importance. That is why Ayestaray et al. *(2)* suggested an algorithm as a help for the therapeutic decision in the differential diagnosis of both pathologic entities when the final diagnosis is yet unclear (Figure 1). The problematic phase is the therapeutic strategy during the period where antibiotics are (not) yet effective and histological diagnosis is uncertain. These authors recommend in case of doubt, Fig 1, Algorithm according Ayestaray et al. This algorithm is a help for the surgical course, but cannot replace the medical discussion for each clinical situation. although immunosuppressive treatment may worsen the evolution of a NF to start with corticosteroids in association with antibiotics. As clinical and biological improvement is noticed after starting corticosteroids and histological results make a NF unlikely the antibiotics could be stopped.

CONCLUSION

One may conclude that is essential to put all the clinical and pathological findings together to make a correct diagnosis. Even done adequately it can still be extremely difficult to become a conclusive result. In our case the blood cultures who kept remaining negative, the first surgical debridement that didn't succeed, the observed violaceous wound margin during revision and the patient's brother who had similar problems after trauma which was treated effectively with corticosteroids are all strong arguments against NF. On the other hand the patient 's medical history, the absence of a systemic disease, the first histological result directing towards NF and the positive medical imaging ensured that the original work up diagnose of NF maintained originally maintained . However the presence of the brother's history ,negative cultures, a positive second histologic report and the violaceous wound margins at the revision in addition with the success of steroid treatment in highly suggestive for the rare diagnosis of Pyoderma Gangrenosum.

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