Necrotizing fasciitis (NF) is a severe, rapidly spreading soft tissue infection of polymicrobial origin. This condition most frequently affects thorax, abdominal wall, extremities, perineum and groin, but according to recent literature the head and neck area is also involved with increasing frequency.

Patients and Methods: Five cases of head and neck NF were detected among patients who were admitted at the Department of Otorhinolaryngology-Head and Neck Surgery of the University Hospital of Patras, Patras, Greece, over a 5-years period. Various parameters including patients’ health status, co-morbidity, etiology, microbiology, affected area, antibiotic therapy, hospital stay, surgical treatment and complications were considered.

Conclusions: The management of NF should comprise of hemodynamic and respiratory evaluation and monitoring, broad-spectrum i.v. antimicrobial therapy, surgical debridement and nutritional support. Close postoperative management of NF patients remains of paramount importance.

Key Words: Necrotizing, Fasciitis, Head, Neck, Streptococcus pyogenes.

Introduction

Necrotizing fasciitis (NF) is a rare, severe, rapidly spreading soft tissue infection of polymicrobial origin that may prove fatal. This infection usually causes widespread necrosis of the superficial fascia and subcutaneous tissue, initially sparing skin and muscles. However, as the disease progresses, thrombosis of penetrating feeding vessels leads to necrosis of the overlying skin and underlying muscles. This condition most frequently affects thorax, abdominal wall, extremities, perineum and groin and in USA approximately 500 new cases are reported annually.

Although the head and neck area is rarely involved, recent reports in the literature suggest that atypical locations of NF like eyelids, periorbital region, face, scalp, ear and neck are becoming more common.

The term necrotizing fasciitis was firstly suggested by Wilson in 1952, although many terms have been used to describe this clinical entity such as hospital gangrene, nonclostridial gas gangrene, hemolytic streptococcal gangrene (Melaney’s bacterial gangrene), necrotizing erysipelas, necrotizing cellulitis, Fournier’s gangrene, necrotizing soft tissue infection, etc.

NF of the head and neck commonly occurs secondary to a dental infection, where the process mainly affects the neck, followed closely by cases with trauma history, usually involving face infection. Sometimes cervical NF may even induced by a common upper aerodigestive tract infection, like pharyngitis or tonsillitis. Many other possible causes have been reported, including peritonsillar abscess, insect sting, burns, surgical procedures, radiotherapy and steroid neck injections. Occasionally, the origin of the infection cannot be detected.

Various systemic diseases with immunosuppressive effects have been considered as pre-existing factors. These typically include diabetes mellitus, acute or chronic renal failure, atherosclerosis, hypertension, hypothyroidism, anemia, HIV infection and malignancy. Moreover, conditions causing impaired immunity have also been involved such as alcoholism, obesity, poor nutritional status, advanced age, drug abuse and corticosteroid therapy. However, there are reports describing fascitis in young, healthy in-
NF has been reported as usually caused by group A beta-hemolytic streptococci and staphylococci. However, using more specialized culture techniques for anaerobic bacteria, it is thought today that this condition is actually the result of a synergistic combination of aerobic and anaerobic pathogens. Early diagnosis of this disease is essential, but not always possible, because the initial presentation may be deceptive. The importance of a definite standardized diagnosis has been emphasized, but is still unattainable because of a significant overlap in clinical presentation and causative bacteria.

High index of suspicion and level of awareness is required to distinguish this infection from other less serious conditions and start prompt treatment. If there is any delay in the diagnosis the infection can rapidly spread producing life-threatening systemic complications and sepsis. If left untreated, NF is associated with high morbidity and mortality rate. The cornerstones of successful treatment include broad-spectrum intravenous antibiotics, aggressive surgical debridement and drainage of all necrotic tissues, intensive supportive care and management of complications.

In the present paper we report our series of NF cases treated in our clinic during the last 5 years and a review of the relative literature.

Patients and Methods

Among patients who were admitted at the Department of Otorhinolaryngology-Head and Neck Surgery of the University Hospital of Patras, Patras, Greece, over a 5-year period (2003-2007), five cases of head and neck NF were detected in our records. In the present study, various parameters such as patients’ health status, co-morbidity, etiology, microbiology, affected area, antibiotic therapy, hospital stay, surgical treatment and complications were considered.

Case 1

A 35-year-old man underwent endodontic treatment of the right lower second molar because of dental caries. The next day he presented fever, headache and tooth pain and received from his dentist oral antibiotics (amoxicillin-clavulanate) and anti-inflammatory treatment (nimesulid). However, swelling of the right side of the face and neck developed over the course of 3 days and the patient exhibited a rapid deterioration of his condition, with high fever, trismus, dyspnea and confusion. Upon admission to our hospital he became septic and collapsed receiving a cardiopulmonary resuscitation. Laboratory findings indicated anemia, an increase in leukocytes ($29 \times 10^9$ white blood cells with 85% neutrophils), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and abnormal hepatic and renal function. Computed tomography (CT) demonstrated diffuse edema of the cheek and neck soft tissues, thickening of the fascial planes and remarkable gas formation (Figure 1). There was a history of heavy smoking, alcohol and drug abuse. Based on clinical and radiological findings, diagnosis of NF was made and the patient was urgently taken to the operating theater for exploration and neck drainage, extensive debridement of any necrotic tissue until healthy bleeding tissue was encountered and tracheostomy under general anesthesia. Actually, there wasn’t any true abscess formation but rather a thin, murky, fluid and dark-brown to black necrotic tissue involving fat, muscles, fascia and small area of skin were found. Histopathological examination of intraoperative specimens reported findings of microthrombophlebitis and necrosis of the affected tissues. Intraoperative cultures
grew group A beta-hemolytic streptococcus (Streptococcus pyogenes), Staphylococcus aureus, Fusobacterium necrophorum and Pseudomonas aeruginosa. The patient received a broad spectrum of antibiotic (vancomycin, piperacillin) and antifungal therapy (collistin, flucozanole) due to the long stay in the intensive care unit along with the appropriate supportive treatment. During this period he underwent four surgical interventions in total for necrotic tissue removal and controlling infection’s spread to surrounding tissues (Figure 2). There was no need for extensive grafting and the wound was left to heal secondarily and finally covered with free skin graft. The patient recovered and left the hospital after 71 days.

**Case 2**

A 42-year-old man, smoker with poor oral hygiene, but without medical history for serious illnesses, was admitted in our clinic for right-sided peritonsillar abscess, mild edema of the ipsilateral neck and trismus. Initially, he received a broad-spectrum empiric antibiotic therapy (amoxicillin-clavulanate and metronidazole) and underwent drainage of his abscess under topical anesthesia. After 24 hours his condition worsened with increase of neck swelling, trismus and high fever. The patient gradually became acidic and hemodynamically unstable. Laboratory tests revealed leucocytosis (18 × 10⁹ white blood cells with 80% neutrophils), elevated CRP and ESR. A CT scan (Figure 3) demonstrated unilateral thickening of the right pharyngeal wall with necrotic areas and air-fluid collections, along with diffuse enhancement and thickening of the fascial planes and muscles of the right neck. A right anterolateral cervicotomy and tracheostomy were performed under general anesthesia for drainage and surgical debridement of any necrotic material until healthy bleeding tissues were encountered. Trauma cultures revealed group A beta-hemolytic streptococcus (Streptococcus pyogenes), Streptococcus viridans, Clostridium sp and the patient received antibiotics (vancomycin, clindamycin) according to the culture results. The trauma was left open for inspection and daily washed with normal saline and hydrogen peroxide solutions until adequate healing occurred and was subsequently sutured in layers. The patient was treated successfully and discharged hospital after 12 days.

**Case 3**

A 72-year-old man was referred to our clinic with a 3-day history of a sore throat and odynophagia followed progressively by fever, cervical pain, left-sided swelling of the neck and mild dyspnea. On oral examination he had an inflamed and erythematous oropharynx with diffuse exudate and a mildly erythematous and swollen, but extremely tender, left side of his neck. On endoscopy, there was a remarkable edema with secretions in the left lateral pharyngeal wall and ipsilateral hemilarynx, reduced mobility of the left true vocal cord and narrowing of the glottis. His medical history included type 1 diabetes mellitus, chronic pulmonary obstruction,
cardiac hypertension and cardiac failure. Blood tests indicated an increase in leucocytes number (25 x 10⁹ white blood cells with 75% neutrophils), elevated CRP, ESR and glucose levels (224 mg/dl) and abnormal liver tests. Ultrasonography depicted lymphadenopathy on the left side of the neck. Administration of broad-spectrum antibiotic therapy including amoxicillin-clavulanate and metronidazole was started. However, patient’s condition rapidly worsened and an urgent CT scan revealed a diffuse edema involving the soft tissues of the neck characterized by loss of clarity in muscular and fascial planes, suggesting also the possibility of fluid collections. Under these circumstances, we decided to surgically explore and drain the patient’s neck with a collar-type incision, performing a tracheostomy at the same time. A thin, grayish foul-smelling fluid was found along the fascial planes, especially at the left side of the neck, with necrotic patches of the fascial layers and adjacent muscles. After adequate drainage and surgical removal of any necrotic tissues, the trauma was thoroughly washed with hydrogen peroxide and left open for daily inspection, washing and debridement. The patient remained for two days on intensive care unit for stabilization and then returned to the clinic. Introperative cultures demonstrated Klebsiella pneumoniae, Bacteroides fragilis and Staphylococcus epidermidis. Thus, culture directed antibiotic therapy (cefazidime, metronidazole) was started instead of the initial empiric antibiotic therapy. There was a gradual improvement in patient’s condition and the trauma healed well and sutured without any need for grafting. Finally, he left the hospital after 18 days without any sequelae.

Case 4

A 45-year-old man, smoker with poor oral hygiene and medical history of rheumatoid arthritis under treatment with corticosteroids and cyclophosphamide, was referred to our clinic for swelling, mild edema of the right side of the neck and trismus. Initially, he received a broad-spectrum empiric antibiotic therapy (amoxicillin-clavulanate and metronidazole).

On oral examination there wasn’t any visible site of inflammation. Endoscopic examination revealed a mild edema of the right hypopharynx and larynx. After 24 hours patient’s condition worsened with increase of neck swelling, high fever and signs of sepsis. Laboratory tests revealed leucocytosis (24 x 10⁹ white blood cells with 80% neutrophils), elevated CRP and ESR. A CT scan (Figure 4) demonstrated areas of necrosis but not organized abscess existence.

A wide cervicotomy (apron flap) and tracheostomy were performed under general anesthesia. The affected areas were drained and debrided. All necrotic tissues were removed until healthy bleeding tissues were encountered. The trauma was left open for daily inspection. The patient was admitted in the intensive care unit of our hospital for 2 days and consequently transferred to our clinic where he underwent washing of the trauma with normal saline and hydrogen peroxide twice daily. Trauma cultures revealed group A beta-hemolytic streptococcus (Streptococcus pyogenes), Streptococcus viridans and Bacteroides fragilis and the patient received antibiotics (vancomycin, metronidazole) according to the culture results. The wound was healed adequately and subsequently sutured in layers without any need for grafting. The patient was discharged from the hospital after 12 days receiving an appropriate course of oral antibiotics.

Case 5

A 50 year-old woman was referred to our clinic with a 4-day history of painful swelling and intense redness of the left side of the neck followed progressively by fever and reduced neck movement. On oral examination she did not have any signs of inflammation. Swelling and erythema of the left side of the neck was extended from supraclavicular area to the mandible. On palpation crepitus was clearly present. Endoscopic ex-
amination did not reveal any important findings. Her medical history included uncontrolled type 1 diabetes mellitus, alcohol and drug abuse. She referred poor socioeconomical status with continuous changes of working and living environment. Blood tests indicated an increase in leucocytes number (16 × 10⁹ white blood cells with 75% neutrophils), elevated CRP and ESR, abnormal hepatic enzymes and high glucose levels (280 mg/dl). Ultrasonography depicted lymphadenopathy in both sides of the neck. A neck CT scan demonstrated diffuse edema of the soft tissues especially on the left side, with thickening of fascial planes and platysma, and small amounts of fluid accumulations. Administration of broad-spectrum antibiotic therapy including amoxicillin-clavulanate and metronidazole was promptly started. However, the patient did not show any signs of improvement and drainage of the affected area under local anesthesia was performed because patient’s refusal for general anesthesia. A thin, foul-smelling fluid was draining and small patches of discolored or nearly necrotic skin were excised (Figure 5). Drainage tubes were left in place. Cultures taken from the pus revealed *Streptococcus pyogenes*, *Streptococcus viridans* and *Clostridium sp* and the patient received antibiotics (vancomycin, clindamycin) according to the culture results.

Patient’s condition improved over the next few days and thus further surgical exploration and drainage was deemed unnecessary. The patient remained in our clinic undergoing washing of the drainage sites twice daily and showed gradual improvement. The drainage sites were sutured, and the patient left the hospital after 20 days under a course of oral antibiotics.

**Figure 5.** Extensive infection and necrotic skin patches of the left neck.

**Discussion**

NF is a relatively uncommon clinical entity involving head and neck area. It is a very aggressive soft tissue infection rapidly spreading along the superficial musculoaponeurotic system (SMAS) and fascial planes, which progressively affects skin or deeper structures.

According to Klabacha et al.⁹, such infections could be classified into four types as follows: type I – consists of a suppurative infection confined to the epidermis; type II – the infection extends to the dermis; type III – the infection extends to the SMAS of the face and superficial layer of the deep cervical fascia; and type IV – the infection affects the musculature. If inadequately treated, this condition can eventually result in major complications, septicemia, multiple organ failure and finally death.

In our series, all patients were classified as infection type II apart from the first patient who was classified as type III.

Some Authors suggested that facial and cervical NF could be considered as distinct clinicopathological conditions with different sources of infection, microbiology, complications and prognosis.⁸ The same Authors reported that between 1945 and 1990 only 67 NF cases had been described in the literature. However, during the last two decades more than one hundred new cases have been reported in the English literature, probably because of the greater awareness of the clinicians for this entity.

The most common cause of cervical NF has been considered to be a dental infection, especially of second and third mandibular molars, encountered in 50% through 80% of the cases in some series. Such infections represent the source of only 11% of cases of facial NF. On the contrary, skin or mucosal injuries have been considered as the major origin of facial NF in approximately 74% of cases, compared to 25% for cervical NF.

A tonsillar or pharyngeal infection has been found to be the cause of NF in less than 15% of cases. Many clinical records have described rare causes of NF such as, acute epiglottitis, parotid infection, intubation, esophagoscopy, adenotonsilllectomy, tracheostomy, laryngectomy, thyroidectomy, herpes infection, acne, furuncles, application of cosmetics, skin biopsy, fish bone ingestion and gunshot wounds. However, 5% of cases remain idiopathic.
In our series only three of the patients had an identifiable etiology. The first case was attributed to infection following endodontic treatment, the second to peritonsillar abscess and the third to pharyngitis. In the other two cases there was no obvious etiology and thus were considered idiopathic.

Associated diseases that can induce immunosuppression have been involved as predisposing factors to NF. Tovi et al\textsuperscript{12} reported that 46\% of patients demonstrated at least one debilitating condition. According to Lin et al\textsuperscript{12}, diabetes mellitus is the most commonly associated disease affecting 72.3\% of the cases in their study, although much lower rates have been reported in other studies (Banerjee et al – 15\%)\textsuperscript{30}. Diabetic patients have decreased number of circulating lymphocytes and T-cells, compromised leukocyte function and antibody response and thus, suppressed immune system, rendering them unable to respond effectively to infection\textsuperscript{33}.

Other common conditions considered to compromise human immunity are hypertension, alcoholism and obesity\textsuperscript{25}. Anemia at initial presentation has also been implicated as a significant factor for NF. Panda et al\textsuperscript{25} state that anemia causes poor wound healing and decrease body resistance to the disease, resulting in an increase of hospital stay by five days in their patients. In our series of patients none exhibited anemia except the first, preventing further conclusions on its effect in wound healing. Nevertheless, NF has been reported to happen in immunocompetent, healthy individuals as well, without any particular disease\textsuperscript{16,17,19,28}.

In our series two of the patients suffered from diabetes mellitus. Other debilitating conditions were present in some of the cases, including chronic respiratory disease and rheumatoid arthritis. Hospital stay for our patients ranged from 12 to 71 days. Four of the patients were hospitalized for 12 to 20 days, while only one had a prolonged admission due to the severity of his condition. The influence of systemic disease on hospital stay and outcome could not be assessed due to the small number of cases. The systemic diseases present in our series of patients are summarized in Table I.

NF has been studied extensively but the exact pathogenetic mechanism of this serious devastating infection has not been yet established. Many researchers have suggested that the pathogens could be \textit{streptococcus} or \textit{staphylococcus}, however, a variety of causative organisms have been reported in the literature considering this condition as a multi-microbial synergistic infection with an increased virulence\textsuperscript{2}.

There is evidence of synergy in laboratory animal studies between \textit{group A beta-hemolytic streptococci} (GABHS) and \textit{staphylococci}. It has been demonstrated in rabbits that staphylococcal lysine can potentiate the action of GABHS in NF\textsuperscript{34}. Furthermore, staphylokinase and streptokinase can activate the release of proteolytic enzymes such as collagenases and hyaluronidase in the subcutaneous tissue resulting to collagen necrosis\textsuperscript{35}.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Smoking, Alcohol abuse, Drug abuse</th>
<th>Systemic disease</th>
<th>Treatment</th>
<th>Hospital stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>None</td>
<td>Fasciotomy, Debridement (4 operations), Drainage</td>
<td>71 days</td>
</tr>
<tr>
<td>2</td>
<td>Smoking</td>
<td>None</td>
<td>Fasciotomy,</td>
<td>12 days</td>
</tr>
<tr>
<td></td>
<td>Debridement, Drainage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Smoking</td>
<td>Diabetes mellitus, chronic pulmonary obstruction, cardiac hypertension, cardiac failure</td>
<td>Fasciotomy, Debridement, Drainage</td>
<td>18 days</td>
</tr>
<tr>
<td>4</td>
<td>Smoking</td>
<td>Rheumatoid arthritis</td>
<td>Fasciotomy,</td>
<td>12 days</td>
</tr>
<tr>
<td></td>
<td>Debridement, Drainage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Smoking, Alcohol abuse, Drug abuse</td>
<td>Diabetes mellitus</td>
<td>Incision, Drainage</td>
<td>20 days</td>
</tr>
</tbody>
</table>
Additionally, as Cromartie et al\textsuperscript{36} reported, streptococcal cell wall mucopeptides when injected into dermal cells can cause necrosis and separation of dermal collagen. This may lead to an aggressive expansion of fasciitis: as the dermis is broken down, the infectious and necrotic process spreads to the epidermis and subcutaneous fat initially affecting tissue just superficial to the deep fascia and subsequently resulting in a rapid and extensive fascial necrosis and subcutaneous destruction, creating an ideal environment for bacterial growth. The process can also include local thrombosis, which induces an environment of low oxygen tension that permits further bacterial growth and ischemic necrosis of surrounding structures\textsuperscript{35}.

Besides, the relative avascularity of the fascial planes and the difficulty of antibiotics to adequately diffuse into the infection site have also been hypothesized to contribute to NF. If not managed properly the necrotic area can quickly expand affect skin, muscles and neighboring structures.

M-proteins of \textit{group-A streptococcus} play also an important role in the pathogenesis of NF. More than eighty different types of M-protein of \textit{Streptococcus pyogenes} can be detected by enzyme electrophoresis\textsuperscript{37}. M-protein is a superantigen in the cell wall responsible for virulence and existence of pyrogenic exotoxins, which can cause fever and shock by inducing synthesis of tumor necrosis factor (TNF)\textsuperscript{38}. Furthermore, it seems that genetic alterations of M-protein could be the cause for higher resistance of some streptococcal strains to cellular and humoral immunity\textsuperscript{37}.

In the majority of NF cases in the head and neck area, reports indicate that this condition results from polymicrobial infection caused by common organisms found in the upper aerodigestive tract, the most frequent being \textit{Streptococcus} species and \textit{Staphylococcus aureus}. According to Elliot et al\textsuperscript{27}, when only a single microorganism is isolated it is usually reported as being \textit{Streptococcus pyogenes}.

Nevertheless, multiple other aerobia and anaerobia bacteria have also been isolated alone or in combination like \textit{Pseudomonas, Proteus, Enterobacter, Enterococcus, Peptostreptococcus, Bacteroides, Fusobacterium, Dipheroides, Prevotella, Klebsiella, Acinetobacter, Clostridium}, etc\textsuperscript{2,14,19,27,31,35}. It is noteworthy that in the literature has been reported a single case with up to 11 organisms being isolated\textsuperscript{39}.

When the origin of infection is dental, usually a wide variety of microorganisms can be found including anaerobes. However, when NF is caused by superficial mucosal or skin lacerations, anaerobes are less probable to grow up and usually the cultures demonstrated Streptococcal and Staphylococcal species\textsuperscript{40}. It has been suggested that the fulminant course of this necrotic process is the result of the symbiotic relationship between aerobes and anaerobes acting synergistically, with the facultative anaerobes growing up on the environment created by aerobes\textsuperscript{31}.

In our cases the cultures revealed a polymicrobial infection including aerobic and anaerobic pathogens. The most common causative pathogen isolated was \textit{Streptococcus pyogenes} (4 cases), followed by \textit{Streptococcus viridans} (3 cases). All causative pathogens isolated in our cases are summarized in Table II.

Although the clinical course of the disease is indistinguishable and the management identical, considering the causative pathogen however, it is of great importance to obtain appropriate bacteriologic specimens on admission of the patient\textsuperscript{14}. At least two sets of blood cultures taken 20 minutes apart and specimens from the wound and pharyngeal swabs must be obtained, ideally before administration of any antibiotic therapy. Microorganisms are best identified when cultures were obtained at the edges of the affected region

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Case No & Bacteriology & Antibiotics \\
\hline
1 & \textit{Streptococcus pyogenes, Staphylococcus aureus, Fusobacterium necrophorum, Pseudomonas aeruginosa} & Vancomycin, piperacillin, colistin, fluozanole \\
2 & \textit{Streptococcus pyogenes, Streptococcus viridans, Clostridium sp} & Vancomycin, clindamycin \\
3 & \textit{Klebsiella pneumoniae, Bacteroides fragilis, Streptococcus epidermidis} & Ceftazidime, metronidazole \\
4 & \textit{Streptococcus pyogenes, Streptococcus viridans, Bacteroides fragilis} & Vancomycin, metronidazole \\
5 & \textit{Streptococcus pyogenes, Streptococcus viridans, Clostridium sp} & Vancomycin, clindamycin \\
\hline
\end{tabular}
\caption{Distribution of patients with NF according to the bacteriology seen in cultures and antibiotics used.}
\end{table}
and not from the necrotic center. Careful interpretation of the cultures’ results is necessary, especially of specimens from open wounds, because contamination is very common. Thus, the most reliable specimens are those taken intraoperatively at a point well away from any open wound. However, because of the polymicrobial nature of NF it is wise to start empiric broad-spectrum antibiotic therapy in high dosage after taking initial blood cultures and wound swabs. Once sensitivities are established, appropriate antibiotics should be instituted ideally after close consultation with the infectious diseases service.

It is remarkable that the overall incidence of positive blood cultures in NF ranges from 25-100%41. Thereby, a significant rate of negative bacterial cultures has also been reported27,30. Lin et al2 reported no bacterial growth in 23% in their series of head and neck NF and Panda et al25 described sterile cultures in five out of 17 cases (29.41%) in their study. Factors such as, technique of collection and identification of pathogen and antibiotic therapy prior to the culturing of bacterial samples could explain the significant rate of sterile cultures noted in these cases.

The recognition of NF may be problematic at the early stages because physical signs and symptoms may be minimal or atypical. This makes the distinction of NF from other conditions like cellulites, erysipelas, wound infection or deep neck infection difficult, thus delaying appropriate management. It is noteworthy, that only 15% of NF patients have the correct diagnosis on admission to the hospital. Early diagnosis is mandatory for successful therapy and minimal loss, in terms of functional and cosmetic deformity5. The diagnosis of NF is mainly a clinical one, therefore a high index of suspicion is required to minimize morbidity and mortality.

Local skin changes are characterized by the signs of acute inflammation, like pain, erythema, swelling, heat and tenderness of the affected area. Pus or fluid may be aspirated or sampled, while crepitus as an indicator of subcutaneous gas, may not be present in all cases. However, its existence along with the aforementioned findings should alert the physician to the possible diagnosis of NF31.

One should have a high index of suspicion for possible NF when there is too much or too little pain of the affected area, the latter probably because of anesthesia due to damage to the surrounding neural structures60. If not suspected, the infection can rapidly spread by necrosis of subcutaneous tissue and superficial fascia and gradually skin, muscle and other structures in a few days. If there is visible skin necrosis at presentation, usually there is much bigger underlying area of subcutaneous necrosis31.

Fever, shortness of breath, tachypnea, tachycardia, dysphagia and odynophagia has also been described as of part of the clinical picture. In advanced stages of the disease, bacteremia, and related exotoxins along with cell death and the release of inflammatory mediators can lead to septic or toxic shock and consequently to multisystem organ failure2,31,35,41.

Because of this dramatic course and outcome, as McMahon et al14 stated, a necrotizing soft tissue infection should be suspected whenever a trivial or clean wound is followed in 12 to 36 hours by prominent systemic signs of sepsis. The same could be suspected for any dental or upper aerodigestive tract infection, with an initial mild presentation, followed by a rapidly deterioration of the patient.

Blood analysis depicts mainly leukocytosis in the majority of NF patients. However, there are also cases with leucopenia, the latter probably being secondary to sequestration of white blood cells within the spleen and lymphatic system, as well as marrow inhibition. Anemia can also be found, as a result of erythrocytes hemolysis due to actions of bacterial enzymes35.

Increased C-reactive protein (CRP) level and ESR, as well as elevation of liver enzymes and blood urea nitrogen levels can be found. Furthermore, hyperglycemia, hypoalbuminemia and hypocalcemia secondary to deposition in necrotic tissues, have been also reported2. The latter results from the binding of ionic calcium with fatty acids from fat necrosis, creating an insoluble soap.

Radiological imaging plays an important role in the diagnosis of NF. Although US, MRI and CT show non-specific signs of inflammation, their contribution in head and neck NF is very helpful when a clinically based diagnosis is not clear. Especially, CT can delineate the extent of the disease or any unsuspected extensions, the relationship with contiguous structures and possibly localize the initial site of infection, providing thus useful anatomic information aiding the surgical intervention49. Occasionally, the CT can explain the discordance between the bad general condition of the patient and the mild local inflammation of the upper aerodigestive tract41.
Specific CT findings are considered being the diffuse thickening and enhancement of subcutaneous fat, cervical fascia and muscles, the presence of gas and the air-fluid level. Although the presence or absence of gas in tissues may be useful in distinguishing NF from cellulitis, however, it is not clear from the literature how frequently this condition is accompanied from gas production. Many Authors have reported that the demonstration of the necrotic colloquative component of the infectious process is a defining and more important clinical feature than that of gas existence. If NF extends beyond neck, common CT signs of thoracic extension could be gas collection, abscess formation, mediastinal widening with enhancement of mediastinal fat, empyema, and pleural or pericardial effusion. Finally, CT should be considered appropriate for follow-up during the course of the disease and treatment.

Histopathology of early lesions demonstrates a superficial epidermal hyaline necrosis, edema and hemorrhage, without inflammatory cells, bacteria or necrosis. On the contrary, advanced lesions is usually characteristic of a widespread inflammatory granulocytic infiltration along with vasculitis and intravascular thrombosis, hemorrhagic areas and necrosis, extending through the skin, subcutaneous tissue and muscles, without, however, evidence of malignancy. There are reports using frozen section biopsy to establish an early diagnosis for NF. In a retrospective analysis Stamenkovic and Lew reported a significant improvement in survival associated with a reduced delay to diagnosis due to this test. This investigation appeared both sensitive and specific and probably is the most accurate diagnostic test for early identification of this condition. However, this test will only be used at an early stage if the clinician has a high index of suspicion considering the diagnosis of NF.

Various complications have been reported in the literature concerning NF. The later the patient treated, the higher the complication rate. Panda et al studied in their study noticed that a delay of more than six days after the onset of symptoms increased the local and systemic complications. Local complications included skin, soft tissue, muscle and bone necrosis (sometimes with permanent mutilation and deformity in the head and neck area), fistula formation (usually pharyngocutaneous), airway obstruction due to excessive tissue edema, hemorrhage due to arterial erosion and internal jugular vein thrombosis. Rarely, very serious vascular complications related to the carotid artery, such as aneurysm, rupture and thrombosis with hemiplegia have been recorded.

Spread of infection to the thoracic cavity further complicates patient management with the potential development of conditions like lung abscess, mediastinitis, pleural infusion, empyema, pericarditis, pericardial effusion, cardiac tamponade, esophageal bleeding or necrosis of the chest wall. Sequestration of a significant amount of fluid occurred in NF may lead to a remarkable hemodynamic response varying from minimal to serious shock. Potential systemic complications of NF include cardiovascular, respiratory, renal and eventually multi-organ failure, electrolyte abnormalities, disseminated intravascular coagulation (DIC) and septic shock.

In our series the patients did not present any serious complications, probably due to the limited extent of necrotic areas and appropriate management of existing co-morbidity. The cornerstone for a successful treatment of NF is prompt diagnosis and treatment without delay. It is noteworthy that many of these patients are delayed on admission to the hospital and some of them require immediate management in the intensive care unit and mechanical ventilation, because they are unstable and already in a septic shock status. Once the diagnosis has been made, it is common practice to start immediately empirical initial therapy with broad-spectrum antibiotics, effective against the most common suspected pathogens. Because of the fulminating course of this infection, it is prudent to avoid delay waiting for culture results.

The regimen should generally include a penicillinase resistant penicillin, usually with an aminoglycoside, for gram positive and negative bacteria coverage and clindamycin or metronidazole for anaerobic. Various other antibiotic combinations have been used successfully as empiric therapy, i.e. benzyl-penicillin along with a third generation cephalosporin and metronidazole or imipenem/cilastatin alone. In our cases we administered amoxicillin-clavulanate and metronidazole as initial empiric therapy.

Even if gram stain demonstrates the presence of gram-positive cocci, it is prudent to continue coverage until the definitive culture results, because of the multi-microbial nature of this condi-
tion. After that, antibiotic coverage can be narrowed to the appropriate dosage adjustments due to possible renal failure of these patients. It is known that penetration of antibiotic into ischemic and necrotic tissue is poor. Thus, conservative therapy alone is ineffective without surgery to control a condition like NF. Aggressive surgical intervention is necessary with wide incision, adequate exploration of deep neck spaces and debridement of all non-viable tissues until normal appearing bleeding tissue is seen in the surgical field. Tracheostomy is usually necessary for airway protection, because tissue edema and necrosis increase the difficulty of intubation. The appropriate placement of incisions is of outmost importance in order to obtain wide access to all extensions of the necrotizing process without compromising the blood supply of the surrounding tissues. Thus, the incisions have to be placed through the skin to the fascia parallel to the cutaneous nerves and blood vessels. The debridement has to be carefully planned, if possible, to preserve as much as vital structures of the head and neck, avoiding thus functional deficits and cosmetic disfigurement.

It is common practice to perform at least 2 procedures, because extension of NF is easily overlooked at the first operation and marginally viable areas may be necrotic in few hours. Usually a second operation is planned in the following 1-2 days and if infection is noted, then a third or more procedures can be performed until no infection can be found. Some Authors suggest a single major debridement followed by multiple minor debridements under local anesthetic once or twice daily if necessary, avoiding repeated general anesthesia. Others suggest re-debridement if the patient remains febrile on antibiotics and NF persists or worsens despite adequate wound care. Necrotic skin also has to be excised along with the underlying areas of subcutaneous and fascial necrosis. However, if the skin is not involved it is preferable to leave the wound open until arrest of the infection and stabilization of the patient. The wounds are packed and changed frequently with wet-to-dry dressings to avoid pooling of secretions and growth of opportunistic infections. After a number of days with stable physiology one could plan for an appropriate reconstruction of the resultant defects. If there are large defects, split-thickness skin grafts will be necessary. Occasionally, advancement or free flaps may be necessary to achieve better cosmetic and appropriate soft tissue coverage.

Other therapeutic measures include management of hypovolemia because of extracellular fluid loss requiring crystalloid administration, intravenous calcium replacement when hypocalcemia exists, correction of other electrolytic imbalances and sometimes blood transfusion when excessive anemia occurs. A controversial issue in the management of NF is the use of hyperbaric oxygen therapy (HBO). It is suggested that HBO acts on the wound to improve healing by killing the infection, increasing tissue oxygenation, promoting angiogenesis, collagen deposition and capillary budding. Thus, improved vascularization of the wound increases penetration of neutrophils, macrophages and antibiotics to the area. HBO is directly cytotoxic to facultative and obligate anaerobes and detoxifies the lecithinase exotoxin responsible for cardiovascular collapse when fulminant sepsis occurs. Until now, no randomized clinical trials have been performed to evaluate the role of this type of therapy in NF, probably because of the infrequency of the condition. Various subexperimental studies have reported a survival advantage. However, all have been performed in a small number of patients with a subjective trend toward improved outcome. Thus, there is no standard HBO protocol for the treatment of NF. Maisel and Karlen suggested a regimen including 1 to 5 dives at 1.5 atmospheres for 30 min every 24 hours. Langford et al. considered an initial treatment of 2.5 to 3 atmospheres for 90 to 120 min, while Mao et al proposed 1 to 2 dives per day per weekday, with each session lasting 45 to 90 min at the depth of 2.8 atmospheres.

In our hospital we have no HBO unit. Nevertheless, we believe that if such an option is available it has its place in the management of NF, especially in more advanced cases, but after appropriate resuscitation, conservative and surgical treatment have been administered without delay. Intravenous IgG (IVIgG) has been used by some Authors for the NF treatment. In a recent study, Norrby-Teglund et al. stated that, the use of a regimen including IVIgG in patients with severe soft tissue infections by Streptococcus pyogenes, could be effective as an initial non-operative approach, limiting the need for immediate extensive debridements in unstable and septic patients. It has been found that IVIgG can neutralize superantigens, reverse the hyper-proliferation...
of the T-cells and downregulate the production of TNF. These features justify its use in superantigen-mediated diseases, like streptococcal toxic shock (STS) and Kawasaki disease. According to Skitarelic et al14 NF may prove to be another indication for this type of therapy, also encountered the low case-fatality rate of IVIgG when treated patients suffering from NF to other sites.

Early recognition of NF is of outmost importance for a favorable prognosis of this potentially fatal condition. Mortality rates vary significantly among series in the literature and were higher in the pre-antibiotics era, while declined dramatically after antibiotics administration (20%-50% versus 9%-33%, respectively)25.

It is also notable that mortality is higher for cervical NF than for the craniofacial one, probably because of spread of cervical infection to the carotid sheath, mediastinum and chest. According to Persaud et al16, mortality in cervical NF is 4 times higher than craniofacial NF. Similarly, Banerjee et al30, in their series found a mortality rate of 19% versus 4.8% and Skitarelic et al41, 32% versus 12.5% for cervical versus craniofacial NF, respectively. Furthermore, in a recent series by Mao et al, survival was 60% if there was thoracic extension of the infection in comparison to 100% in patients without chest involvement40.

Many other potentially independent variables have been significantly associated with an increased possibility of worse prognosis and death in NF patients. Elliot et al17, in their series demonstrated a number of such aggravating factors including, age over 60 years which had 5 times higher mortality, female gender, pre-existing systemic disease, renal impairment, elevated serum lactate levels, late surgical intervention, initial site and extent of infection and the degree of organ system dysfunction at admission. Uncontrollable diabetes with ketoacidosis, impaired immune competence and septicemia within 24 hours have also been considered as critical factors for a fatal outcome25.

To summarize, the management of NF should comprise of hemodynamic and respiratory evaluation, resuscitation and monitoring, adequate bacteriologic specimen, high dose broad-spectrum i.v. antimicrobial therapy, surgical excision and debridement, nutritional support and possible HBO. Appropriate and close postoperative management of NF patients is of outmost importance and can be challenging and difficult, depending at the patient’s response to therapy and the associated co-morbidities14.

References

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