Case Report

Necrotizing fasciitis – a complication of autoimmune skin blistering diseases?

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Abstract
Introduction: Autoimmune bullous diseases (AIBD) are organ-specific skin blistering diseases clinically manifesting as bullae and vesicles of the skin and mucous membranes. The loss of skin barrier integrity renders patients susceptible to infection. Necrotizing fasciitis (NF), a rare yet severe infectious complication of AIBD has been insufficiently documented in the literature.
Case report: We present a case of a 51-year-old male patient with NF initially misdiagnosed as herpes zoster. Given the local status, CT imaging, and laboratory parameters, NF diagnosis was made and the patient was taken for an urgent surgical debridement. In a further development, new bullae in remote areas erupted and a perilesional biopsy, direct immunofluorescence as well as local status, the patient's age, and atypical presentation, imposed an initial diagnosis of epidermolysis bullosa acquisita. Differential diagnoses were bullous pemphigoid (BP) and bullous systemic lupus. In the literature, 9 other described cases were found and are reviewed.
Conclusions: Due to its unspecific clinical picture, necrotizing fasciitis itself presents a frequently misdiagnosed soft tissue infection. Altered laboratory parameters in immunosuppressed patients often lead to misdiagnosing of NF and loss of precious time, which plays a major role in survival. Given the manifestation of AIBD as loss of skin integrity and immunosuppressive therapy, these patients could be more predisposed to NF than the general population.

Key words: fasciitis; bullous pemphigoid; immunosuppression; epidermolysis bullosa acquisita.

Introduction

Autoimmune bullous diseases (AIBD) are organ-specific skin blistering diseases clinically manifesting as bullae and vesicles of the skin and mucous membranes [1]. For bullous pemphigoid (BP), the most common subepidermal AIBD, the incidences were estimated to be 7.63 per 100,000 person-years in a recent study [2]. The loss of skin barrier integrity renders patients susceptible to infection. With many new therapeutic guidelines on the horizon, therapy still mostly relies on unspecific immunosuppression, such as potent topical and systemic corticosteroids. However, complications and infections in these conditions haven't been systematically studied in the literature. Necrotizing fasciitis (NF), a rare yet severe complication has been insufficiently documented among AIBD patients. Colloquially called "flesh-eating disease", NF is a rare necrotizing soft-tissue infection [3]. Mortality rates of necrotizing fasciitis have been reported as high as 76% [4]. The most common risk factors for NF include trauma, from minor such as injections to major such as surgery, diabetes mellitus, immunodeficiency, chronic heart failure, obesity, and peripheral vascular disease [5,6], sharing many of the risk factors for poor outcome found in AIBD patients. Due to its unspecific clinical picture, necrotizing fasciitis itself presents a frequently misdiagnosed soft tissue infection [7]. It is thus plausible that such complication in AIBD patients is underreported and the risk of necrotizing fasciitis in these patients is underestimated. Due to the low frequency of both AIBD and NF cases, the ability to make a significant correlation could be difficult for investigators.

Here we present a patient with AIBD complicated by necrotizing fasciitis and a review of previous reports in the literature.

Case Report

A 51-year-old male patient was admitted to our institution presenting with extensive necrosis of the right side of the thoracic wall and sepsis. Before his arrival at our hospital, he has been transferred to three

different tertiary institutions. On admission, the patient was in a stuporous state, highly febrile, tachycardic, tachypneic, unresponsive, pale, and severely dehydrated. Other local findings showed a diffuse septic rash, and signs of epidermolysis in a resolution presented on the palms, the left axillar, and the anogenital region. Arms were covered with diffuse oval, immature, and mature hypothrophic scars. Nasal and oral mucosa, as well as conjunctiva, were unremarkable. Deep tissue necrosis was affecting the right hemithorax, total body surface area was estimated at 10% (Figure 1). Crepitations under the surrounding erythematous skin were also present. As per obtained information, initial symptoms started 3 weeks prior as bullae in the affected dermatome. Acyclovir tablets were prescribed by his primary healthcare provider due to suspicion of Herpes zoster. The patient remained refractory to treatment and herpes zoster infection was later excluded by an infectious diseases specialist. Erythema, pain, and fever followed the week prior to hospitalization. From the patient's medical history, unspecified data on previous corticosteroid therapy was obtained, as well as information about diabetes mellitus type II on OADT. Laboratory results on admission showed blood glucose levels of 18.3 mmol/L and HbA1c > 14%. Markers of inflammation revealed a white blood cell count of 24.8×10^9/L, C reactive protein 301.6 mg/L, LDH 783 U/L, and procalcitonin 1.320 ng/ml. An electrolyte disbalance was found with a sodium level 116 mmol/L, and a potassium level of 5.4 mmol/L. Other laboratory findings showed serum

hemoglobin 121 g/L and serum albumin 19 g/L. Computed tomography (CT) showed necrosis of the left hemithorax surrounded by fat stranding and lymphadenopathy. Given the CT imaging, laboratory, and local findings, a necrotizing fasciitis diagnosis was established and an empiric antibacterial therapy of vancomycin, clindamycin, and meropenem, was immediately administered. The patient was taken for an urgent surgical debridement in the operating room and placed in the intensive care unit for extensive monitoring. Wound cultures showed *Acinetobacter* spp, *Klebsiella-Enterobacter* spp., *Pseudomonas aeruginosa,* and *Enterococcus* spp., while routine skin swabs of unaffected areas found *Acinetobacter* and *Enterococcus* colonization. Antimicrobial therapy was corrected as per the antibiogram, and colistimethate sodium was added. In a preoperative evaluation, chest radiography revealed pulmonary infection and pleural effusion with a peculiar incidental finding of tracheal stenosis. Such findings in conjunction with the aforementioned epidermolysis of anogenital, palmar, and axillar regions, as well as the oval scaring of the arms, imposed an AIBD hypothesis. In a further development, new bullae in remote areas erupted and a perilesional biopsy of a sample from the right thigh showed subepidermal blistering with a paucicellular infiltrate mostly consisting of lymphocytes. Direct immunofluorescence showed linear IgG and C3 complement deposition on the dermal-epidermal junction (Figure 2), while the indirect immunofluorescence on rat bladder transitional epithelium was negative. Given the patient's relatively young age, atypical clinical presentation, and mucosal involvement, the initial diagnosis of epidermolysis

Figure 1. On admission: Immature and mature oval hypothrophic scars on the forearm, indicating recent and late previous episodes of subepidermal AIBD. An important clue in the absence of anamnestic data. NF affected skin necrosis and surrounding erythema on the left hemithorax.

Figure 2. Blister formation at the dermal-epidermal junction and IgG antibody deposition.
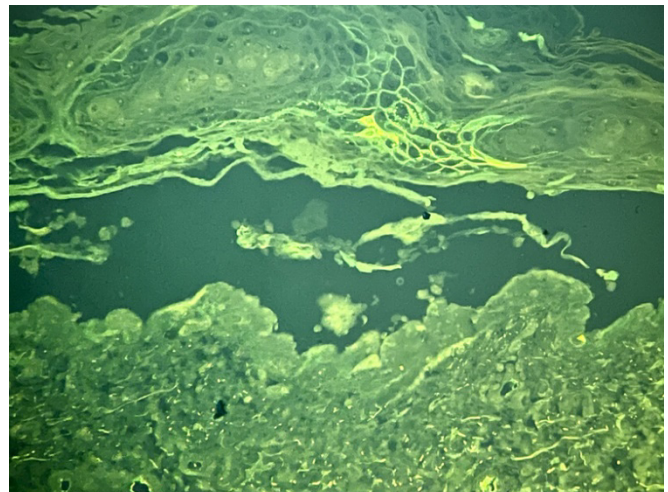
bullosa acquisita was made [8]. Differential diagnoses included bullous pemphigoid and bullous systemic lupus. Regular successive surgical debridement was performed due to rapid necrosis advancement in healthy surrounding tissues (Figure 3). The patient's condition worsened due to multidrug-resistant *Acinetobacter baumanii* complex sepsis. Intravenous immunoglobulins (IVIG) were considered and serum immunoglobulins showed low levels of IgG and IgM, with a slightly elevated IgA. Unfortunately, the patient died before their administration and further investigation.

Discussion

In our search of subepidermal AIBD complicated by NF, patients with BP were searched and 6 case reports were found with a total of 9 patients, presented in Table 1 [9–14]. The mean age of this case series, including our patient, was 71.5 years, ranging from 51-86 years old. All cases reported had incomplete control of the disease and an active bullous eruption at the time of NF diagnosis. The correlation between NF and diseases requiring immunosuppressive therapy has been previously described in studies of other autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and scleroderma [15,16]. Corticosteroids impact both innate and acquired immunity with their effects proven to be dose-dependent [17,18]. One retrospective multicentric study found prednisolone doses greater than 37 mg/d at discharge a significant risk factor for lethal outcomes in AIBD patients [19], thus testifying that these patients are indeed immunocompromised. Among individuals

Figure 3. After several debridements. Advancement of necrosis and infection in the surrounding tissues.

in Table 1, in most cases, the NF complication arose in the first month following the initiation of treatment. Doses of oral corticosteroids reported in Table 1 varied from 30-100 mg daily, given as a monotherapy or combined with other immunomodulatory agents (IMA). Other patients were treated with topical corticosteroids, exclusively or combined with other IMA.

Most frequent pathogens isolated were *Streptococcus* group A (7/10), methicillin-resistant *Staphylococcus aureus* (MRSA) (3/10), and *Acinetobacter* spp. (2/10), in Table 1. Necrotizing fasciitis type I is a polymicrobial infection usually described following trauma, caused by aerobe and anaerobe bacteria, most frequently associated with immunocompromised individuals as well as diabetic

Table 1. Literature review of bullous pemphigoid cases complicated by necrotizing fasciitis.

Authors	Age	Sex	Comorbidities	NF onset after diagnosis of BP	Control of BP	Previous therapy	Current therapy	NF onset after initiation of current therapy	Diagnostics	Skin colonization	Bacteriology	NF treatment	Evolution
Chamberlain 2003	85	F	HTA	16 days	Incomplete	TCP, Erythromycin 250 mg × 2	Prednisolone 30 mg/g + Betamethasone 500 µg × 2/d mouth wash, Erythromycin 250 mg × 2	9d	Local findings of NF on the left leg, laboratory, Microbiology, Ultrasound	?	Strep A	Successive surgical debridement, split thickness skin grafting, Initial antimicrobe therapy: Vancomycin 1 g × 2, Meropenem 1 g × 3, Additional antimicrobial therapy: cefuroxime 1.5 g × 3, clindamycin 300 mg × 4	Survived (sequel)
Boughrara 2010	73	M	MI, benign vesical polyps	2 years	Incomplete	?	TCP	2 years	Local findings of NF in two localizations: left arm and dorsal side of the right hand, Microbiology	*S. Aureus*	Strep A, *Pseudomonas* sepsis	Debridement of the left arm and amputation of the right index finger. Antimicrobial therapy undisclosed.	Died
Boughrara 2010	64	F	Obesity, insulin dependent DM	2 months	Incomplete	?	TCP, MTX 15mg/week	14d	Local findings of NF on the left leg, microbiology	?	Strep A, MRSA, *Acinetobacter*	Surgical debridement of the dorsal side of the foot and amputation of two toes. Antimicrobial therapy undisclosed.	Died
Boughrara 2010	81	M	HTA, insulin dependent DM, preterminal CRI, COPD	7 months	Incomplete	TCP	TCP, MMF	14d	Local finding of NF on left leg and foot, Microbiology	?	Strep A	Surgical debridement, Antimicrobial therapy undisclosed.	Died
Doffoel-Hantz 2011	86	F	Acheimer's dementia	5 weeks	Incomplete	TCP	TCP	3 weeks	Retiform purpura of the ankle followed by development of necrosis.	?	Strep A	Broad-spectrum antibiotics, no surgical debridement was performed.	Died
Ekiz 2013	78	F	HTA	1 year	Incomplete	Tetracycline, Niacinamide, TCP, systemic steroids	Prednisolone 48 mg/d after 2 weeks 32mg/d,	3 weeks	Local finding of NF on the left leg, laboratory, MRI, Microbiology, Histopathology	?	Strep A.	Surgical debridement, Sulbactam/ampicillin 1 g, oral ciprofloxacin 750 mg 2 × 1, tigecycline	Died
Sene 2014	52	M	Obesity	?	Incomplete	TCP	Prednisolone 100 mg/d, after 2 weeks Prednisolone 60 mg/d and MMF 2mg/d	35d	Local finding of NF on the left leg, laboratory, Microbiology	?	Strep A	Surgical debridement, pipera-cillin-tazobactam and vancomycin	Survived
Sene 2014	76	F	HTA, DM	8 months	Incomplete	TCP 30 g/d	TCP 10 g/d, MMF 2 g/d	2 weeks	Local finding of NF on the left leg, laboratory, Microbiology	?	Strep A, MRSA	Surgical debridement piperacillin-tazobactam, gentamicin, and vancomycin	Died
Noguchi 2018	69	F	DM,	2 years	Incomplete	Prednisolone 20 mg/d, Cyclosporine 100 mg/d	Prednisolone 40 mg/d, IVIG 4 days latter	4 d	Local finding of NF on the insertion point of CVC, Laboratory, Microbiology, CT scan	MSSA, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Enterobacter* spp.	MSSA	Surgical debridement piperacillin-tazobactam and vancomycin	Survived
Jurisic 2022	51	M	HTA, DM, Obesity	?	Incomplete	Undisclosed corticosteroid therapy regimen	?	3 weeks	Local finding of deep tissue necrosis due to advanced disease, laboratory, microbiology	*Enterococcus* spp. *Acinetobacter* spp.	*Acinetobacter* spp. *Klebsiella-Enterobacter* Spp. *Pseudomonas aeruginosa*, *Enterococcus* spp., *Acinetobacter baumannii* complex (MDR)	Successive surgical debridement, Vancomycin 2 × 1.5 g, Clindamycin 900 mg 3 × 1 and Meropenem 3 × 1 g. Additional antimicrobial therapy: Colistimethate-sodium 3 × 3 000 000IU	Died

Strep A: Streptococcus group A; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-sensitive Staphylococcus aureus; TCP: topical clobetasol propionate 0.5%; HTA: hypertension; MI: myocardial infarction; MTX: Methotrexate; CRI: chronic renal insufficiency; COPD: Chronic obstructive pulmonary disease; MMF: Moeftil mycophenolate; MRI: magnetic resonance imaging; CVC: central venous catheter; MDR: multi-drug resistant.

patients. Type II infection is a monomicrobial infection most frequently caused by *Streptococcus* group A and MRSA. It often presents spontaneously, without previous trauma, possibly by systemically seeding from transient bacteremia from nasopharynx due to asymptomatic pharyngitis [20]. Our patient series shows a predominance of monomicrobial NSTI. This could potentially justify taking routine nasopharyngeal swab tests in AIBD patients before initiation of immunosuppressive therapy. Skin colonizing bacteria from routine swab tests in AIBD patients with NF infection are also presented in Table 1, though providing insufficient information. As for AIBD therapy, a study from 2002 [21] by Joly *et al.* showed that in patients with moderate and extensive disease, topical 0.5% clobetasol propionate (TCP) is equally potent as systemic corticosteroids with longer overall survival and fewer severe complications. In this report, two patients received topical corticosteroids as monotherapy, without sufficient data on previous cumulative corticosteroid doses and consequently, immunological status.

The most common comorbidities described in this review were diabetes mellitus, hypertension, and obesity. Diabetes mellitus is found to be the most common underlying condition in NF, reported in 44.5% of patients [7], and an individual risk factor for a poor outcome in AIBD patients in some studies [22]. It's important to keep in mind that it is also the most common adverse effect of corticosteroid therapy and can subsequently develop during any stage of the treatment. One group of authors expressed that 40% of all inpatient endocrinology consultations in their hospital are steroid-induced new-onset diabetic patients [23].

NF is found to have a more fulminant course in immunocompromised patients than in the general population, as occurred in most of the presented cases. Mortality rates of NF have been reported as high as 76% in the literature [40]. In this reported series, 70% of patients (7/10) had a fatal outcome. A study assessing immune status in NF patients found that mortality was significantly higher in immunocompromised than in immunocompetent patients. Moreover, diagnosis and first surgical debridement were more often delayed in immunocompromised patients compared to the control group [24]. Another study found that mortality rates were 9 times higher if surgical debridement was delayed more than 24 hours after the onset of symptoms [25]. Survival in these patients relies on timely diagnosis, still, NF was misdiagnosed in approximately 70% of patients according to the meta-analysis by Goh

et al. [7]. Unfortunately, our patient also lost precious time being transferred to several tertiary institutions before arriving at our hospital.

In 2004 the laboratory risk indicator for NF (LRINEC) score was developed by Wong *et al.* [26] as a helpful diagnostic tool for clinicians, based on the use of routinely obtained parameters: white blood cell count, hemoglobin, glucose, creatinine, sodium, and C-reactive protein. In immunocompromised individuals, due to myelosuppression, laboratory findings can show low white blood cell count, hematocrit, and platelet count as well as normal or mildly elevated C-reactive protein possibly compromising the results of LRINEC scoring, posing another major obstacle in early diagnosis in these patients [24,27]. The most common symptoms of NF are soft-tissue edema, erythema, tenderness, fever, skin bullae, and necrosis, in advanced disease. The most important clinical symptom is pain increase disproportionate to local findings [20,28]. The use of antipyretics in hospitalized patients such as ibuprofen can attenuate pain, diminishing another important clinical sign. Imaging tests such as magnetic resonance imaging and CT scans are useful tools in diagnosing and evaluating the depth of infection, though their use in diagnosing NF is debatable, especially if performing these tests leads to a delay in surgery [20]. Aggressive antimicrobial therapy covering gram-positive, gram-negative, and anaerobic bacteria, such as piperacillin-tazobactam, vancomycin, and meropenem should be administered empirically as soon as possible [20,29]. Immunocompromised patients with NF should be urgently managed by a surgical team experienced in handling such patients [29].

Some studies have found skin and soft tissue infections to be one of the most common causes of morbidity and mortality in AIBD patients [22,30]. So far, only one study found a statistically significant correlation between the risk of NF and AIBD, due to its uniquely large patient sample size. In 13.297 and 6.294 patients with primary and secondary diagnoses of BP respectively, both groups of patients were associated with higher odds of NF. Additionally, associations of any serious infection in both AIBD patients were lower median household income and government or no insurance, showing an increased susceptibility to such complications in patients of lower socio-economic status [31]. Accurate reporting of such adverse infectious complications is imperative in further research on risk, prevention, and management of NF in skin blistering disorders. Many protocols have been developed for the management of infections in cancer or transplant patients. Possibly due to low incidences of

bullous dermatoses, no protocols have been designed especially for these individuals. Until further studies, signs of edema, erythema, crescendo pain, fever, skin bullae, or necrosis, followed by tachycardia, acidosis, or hyperglycemia should raise high suspicion of NF in treating clinicians and a multidisciplinary approach is deemed necessary.

Conclusions

AIBD shares many known risk factors for NF such as loss of skin barrier, immunosuppression, and diabetes, thus these patients could be more likely to develop NF. With new cases emerging, clinicians should be aware of these possible infectious complications. Accurate reporting of these cases is imperative for further research. Signs of erythema, edema, fever, and disproportionate crescendo pain to local findings followed by changes in laboratory parameters should raise high suspicion of NF in AIBD patients.

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