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Necrotizing Fasciitis: An Overview and 2 Illustrative Cases

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Abstract

Necrotizing fasciitis is the generic term for a series of progressive gangrenous infections of the skin and subcutaneous tissues. Typically, necrotizing fasciitis start with an, often small, infected lesion with atypical symptoms, which then quickly develops into a rapidly spreading, massive infection. The primary therapy is excision of all necrotic tissue in combination with treatment of systemic symptoms such as shock. The defects resulting from rigorous excision are often very large. Once they are clean, they require closure with an autograft. This article reviews the symptoms and treatment of necrotizing fasciitis. In addition, it illustrates, with 2 cases, how a hyaluronic-based extracellular matrix can be used to "fill in" with neodermis for the lost dermis and can create a wound bed most suitable for grafting.

Keywords

hyaluronic acid, necrotizing fasciitis, diagnosis, treatment, extracellular matrix

Necrotizing fasciitis (NF) is, primarily, an infection of the fascia and may spread rapidly to other subcutaneous tissue as well as to the skin. It is the currently accepted generic term to encompass into a single category of diverse syndromes of progressive gangrenous infections of the skin and subcutaneous tissues.[1] While NF is commonly caused by *Streptococcus* type A or *Staphylococcus aureus*,[2] most bacteria are, in fact, capable of causing the disease,[3,4] and polymicrobial infections also may occur.[5] Although more common in adults, NF also affects the pediatric population.[6,7]

Typical (initial) clinical symptoms of NF include (serious) pain, erythema, and skin necrosis with or without bullae. Systemic symptoms include those commonly associated with an infection but often rapidly progress to the symptoms of septic shock.

Because of the rapid progression of the disease, with infection and necrosis swiftly spreading from one anatomical structure to another, radical, urgent, and often extensive surgical debridement is required—the timing of intervention is directly linked to morbidity and mortality.[8] Reconstruction is challenging, particularly when large excisions were necessary.

This article describes the treatment and outcomes of 2 patients with NF, treated with (sequential) excision, an esterified hyaluronic acid (HA) matrix (eHAM), and partial thickness skin autografts (STSGs). The article also discusses diagnostic and treatment options and guidelines, as well as risk factors.

Cases

Patient 1 (Figures 1-4)

Patient 1 is a 55-year-old female, without any preexisting conditions. Seventy-two hours after a motor vehicle accident, she presented to the emergency room with a very painful contusion of the left foot and symptoms of (septic) shock (temperature = 98.3°F [36.8°C], pulse rate = 109 beats per minute, respiration rate = 18 breaths per minute, blood pressure = 75/47 mm Hg, C-reactive protein = 412, and white blood cell count = 21.6 × 10^9/L) and the clinical signs of NF of the left foot and lower extremity. Shock treatment was initiated, and the patient underwent radical excision with Bovie cautery (Bovie Medical Corp, Clearwater, FL)—in total, 200 cm^2 of necrosis was removed from the foot and 900 cm^2 from the lower leg. Cultures were positive for *Streptococcus* Group A, which was treated with intravenous antibiotics. Further debridement was necessary on day 7 postinjury and on day 9 when excision to the left adductor muscles of the thigh was performed. In total, an additional 2.200 cm^2 of tissue was excised.

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Figure 1. Patient 1. Initial aspect of infected left foot. Often, the subcutaneous infected area is significantly larger than the infected skin shows.

Figure 2. Patient 1. Radical excision (day 9; second excision) is necessary.

Figure 3. Patient 1. Esterified hyaluronic acid matrix in situ.

Figure 4. Patient 1. Postinjury day 94. Complete reepithelialization after STSGs were applied over esterified hyaluronic acid matrix. Acceptable cosmetic results.

Washouts with saline were performed until the wound bed was ready to be grafted with eHAM on the 24th day postinjury. eHAM was covered with conventional, bulky dressings, which were changed every second day.

Thirty-eight days after the accident, with pre-albumen at 20 mg/dL, eHAM was completely incorporated into the wound: the silicone top layer was removed, and the lesion was covered with an STSG, procured from both medial thighs and the abdomen. The graft was meshed 1.5:1 to allow for drainage. Both the recipient site and the donor site were dressed with Xeroform (DeRoyal, Powell, TN).

The donor sites healed within 7 days. At 44 days after the accident, graft take was 100% (6 days after the grafting procedure), and the patient was discharged. At 94 days after the incident, the lesion was judged to be completely healed and cosmetically acceptable.

Patient 2

Patient 2 is a 53-year-old male, suffering from lymphedema, varicosis on both legs, hypertension, super-obesity (body mass index = 55 kg/m^2), and a small venous ulcer on the right lower leg, which was licked by his cat. Sixteen days after the licking incident, the patient presented with a painful, draining wound and a temperature of 98.2°F (36.7°C). The heart rate was 131 beats per minute, respiration was 17 breaths per minute, the blood pressure was 145/64 mm Hg, and white blood cell count was 11.1×10^9/L. The patient was admitted under the suspected diagnosis of NF for observation and the administration of IV antibiotics. The wound and the patient's general condition deteriorated, and on day 19 "post licking incident," 247 cm^2 of necrosis was excised from the right lower leg. Re-resections were performed on each of the next following 5 days: in total, 9.297 cm^2 of necrosis were excised. Blood cultures were positive for *Pasteurella multocida* and methicillin-resistant *Staphylococcus aureus*; these were treated with IV antibiotics.

The patient and his wound condition gradually improved, and on the 32nd day after the first excision, eHAM was applied on a granulating wound bed. The matrix was treated topically with Prontosan gel.

When the eHAM was incorporated (day 47), the top layer was removed, and the wound was covered with an STSG, meshed at 1:1.5, taken from the contralateral thigh, with a second STSG applied on day 81 because of incomplete take of the first graft. Both the donor site(s) and recipient site(s) were covered with Xeroform. On day 87, the donor sites had completely reepithelialized and graft take was 100%. Donor sites and recipient sites were judged to be cosmetically acceptable.

Discussion

Symptoms and Diagnosis

Necrotizing fasciitis usually starts as a painful, but otherwise unsuspicious, lesion. Early diagnosis is critical, however, so that the preferred therapy, excision of all dead and infected tissues, can start as early as possible. Early symptoms are not very specific, however, and may include pain, erythema, and, somewhat later in the course of the infection, skin necrosis with or without bullae. Initial fever usually becomes serious within the first few days. Painful cellulitis (44/46), skin necrosis (26/46), skin blistering (8/46), and subcutaneous emphysema (3/46) were the most common symptoms in a study performed in the United Kingdom.[9] Another study showed skin erythema and swelling at the affected site (97.6%), pyrexia (61.9%), hypotension (33.3%), altered consciousness (28.6%), bullous lesions (26.2%), and crepitus (9.5%) as the most common clinical manifestations within the first 48 hours after the initial (suspected) diagnosis.[10]

Systemic symptoms include those commonly associated with an infection and septic shock with laboratory tests characteristically showing results typical for an infection.

NF is commonly caused by *Streptococcus* type A: in a Swedish study, 87% of infections were monomicrobial and mostly caused by Group A streptococci. In this setting, the use of the rapid antigen-detection test for Group A streptococci was shown to help in shortening the time to surgical intervention.[11] *Staphylococcus aureus* infections[2] also are a very common cause for NF but many (monomicrobial or polymicrobial) bacterial infections may lead to the diseases.[5]

Gram stain and, in some doubtful cases, frozen-section tissue biopsy may assist in confirming the bacteriological diagnosis.[1,12] Different ways of imaging (ultrasound,[13] magnetic resonance imaging[14]) are very useful not only to confirm the diagnosis of the disease but also to assess the extent of the disorder, plan the surgical excision, as well for the detection of underlying etiologies. The presence of gas within the necrotized fasciae is characteristic but may be lacking. The main finding is the thickening of the deep fasciae due to fluid accumulation and reactive hyperemia, best seen on magnetic resonance imaging.[14]

Risk Factors and Prognosis

In one US-based study, ethnicity was shown to play a role with regard to NF-related mortality, which, according to the authors, merits further investigation.[15] Patients with diabetes mellitus show a higher complication rate and increased mortality.[5,16] Obesity was also found to contribute to mortality,[5] although interestingly enough, another study showed a low body mass index (as well as a preexisting chronic kidney disease) to be associated with increased mortality rates.[17]

A higher LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) severity score[18] (>4 points), hypotension, altered consciousness, respiratory failure requiring ventilator support, elevation of alanine aminotransferase levels >2-fold, serum creatinine >177 μmol/L, thrombocytopenia ($<100 \times 10^9$/L), and worsening symptoms and signs within 48 hours of admission were also associated with higher fatality rates ($P < .05$).[10]

An important aspect of the high mortality risk is caused by initial misdiagnosis or delayed but proper diagnosis.[19] The diagnosis is primarily a clinical one: it often is missed in the early stages of the disease because of the difficulty in differentiating it from more common soft tissue infections such as cellulitis or erysipelas.[20,21] Time from admission to operation was shown to be critical: the average time to operation was 90 hours in nonsurvivors versus 25 hours in survivors ($P = .0002$).[22] In another study, it was shown that more than one comorbidity, thrombocytopenia, anemia, more than 24-hour delay from onset of symptoms to surgery, and age greater than 60 years were independently associated with mortality.[23] Among IV drug users, the incidence of NF also is on the rise.[24]

The mortality rate of NF in the United States between 2003 and 2013 was found to be 4.8/1 000 000 person-years.[15] Mortality in another US study published in 1996 was as high as 73% and, depending on the type of NF, may still reach up to that percentage.[25] In a single study in Australia, the most commonly involved sites were the perineum (33.7%), lower limb (29.9%), and trunk (18.2%).[5] In a study from New Zealand, the amputation rate in patients with NF of a limb was quoted as high as 16%.[26]

Fournier's gangrene is a specific type of NF where the genitalia and peritoneum are involved. It has an even higher mortality rate[27]: case series analyses have shown a mortality rate of 20% to 40% with an incidence of as high as 88% in some reports.[28]

Treatment

Because of the complexity of the disease itself as well as the required treatment of both the necrosis and the systemic

complications of the disease, many NF patients, as well as patients with other necrotizing soft tissue infections, are now being treated in burn centres.[8,29,30]

The initial administration of wide-spectrum IV antibiotic therapy followed by a more specific therapy, guided by the outcomes of bacterial cultures,[1,11] is an essential part of treatment, as is shock prevention and treatment, treatment of complications (ie, kidney failure), and restoration of electrolyte and fluid balance.

Early recognition and surgical intervention are of crucial importance: the single most important treatment step is removal of all necrotic tissues.[12,30-33]

The results of hyperbaric oxygen treatment during the initial excisional stages of the disease are not conclusive,[5,34,35] but negative-pressure wound therapy has been used successfully after the excision stages to optimize wound healing and facilitate application and fixation of skin grafts.[36,37]

Patients who survive the infection require extensive treatment of the excised area and the resulting full-thickness lesion, including reconstructive surgery with sometimes marked sequelae related to the extent of fasciitis and debridement.[19] The use of extracellular matrix (ECM)-type products may play an important role in the reconstruction phase: replacement of a lost ECM serves both the speed as well as the overall quality of healing, as proven in many indications.[38,39] Several distinct types of ECMs, based on different compounds obtained or derived from natural or bioengineered ECM, some of them populated with cells, have become available.[40-43] Many have been shown to provide fast recovery and better skin quality after being used after massive excisions.[8,12,44]

HA (hyaluronan) is an anionic, non-sulfated glycosaminoglycan compound, present in the normal ECM. It plays an essential role in wound healing by facilitating and directing cell proliferation,[45] as well as fibroblast migration,[46] stimulation of angiogenesis,[47] and many other processes involved in healing.[45] HA is difficult to handle and has a short half-life. Esterification, a modification, facilitates handling and practical usage of the product by increasing the half-life.[48]

eHAM, a soft, nonwoven mat of fine fibers, is a biodegradable dermal matrix contact layer, made of Hyaff (Medline Industries, Northfield, IL), a specific type of esterified HA. eHAM has a semipermeable silicone outer layer for physical protection of the wound and controlling water vapor. The matrix acts as a scaffold for cellular colonization (eg, by fibroblasts) and capillary ingrowth. Once granulation tissue has developed, the silicone layer is peeled off and the resulting wound bed can be grafted. The matrix has been used successfully as an ECM in a number of different indications.[46,49-55]

In the 2 cases described here, full-thickness excisions were performed and eHAM was used successfully to create a wound bed, suitable for coverage with a split skin autograft. This shows that massive excisional lesions can be treated in such a way that cosmetically acceptable results can be obtained.

Case histories do not provide scientific proof for the efficacy of a treatment and only a limited amount of information is available on the role of commercially available ECMs in the treatment of excised NF necrosis.[8,44,56] This article is not meant to provide such proof, however. Rather, it demonstrates how systemic treatment of NF, in combination with massive excision of all necrosis and followed by the application of eHAM, may lead to relatively rapid healing with acceptable cosmetic results.

Proper treatment of NF consists of antibiotic therapy, prevention or treatment of the systemic effects of the infection, i.e., shock, and rapid removal of all necrosis and infected tissue. This creates a full-thickness (or even deeper) lesion. Once the wound and the patient have recovered to a healthier status, reconstruction of the excised areas can be initiated. In the 2 patients described here, eHAM was shown to contribute to a wound bed, appropriate for grafting, as indicated by the graft take, and to acceptable cosmetic results on complete reepithelialization.

Declaration of Conflicting Interests

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References

1. Patiño JF, Castro D. Necrotizing lesions of soft tissues: a review. *World J Surg*. 1991;15:235-239.
2. Jamal N, Teach SJ. Necrotizing fasciitis. *Pediatr Emerg Care*. 2011;27:1195-1199.
3. Persichino J, Tran R, Sutjita M, Kim D. *Klebsiella pneumoniae* necrotizing fasciitis in a Latin American male. *J Med Microbiol*. 2012;61(pt 11):1614-1616.
4. Adachi M, Tsuruta D, Imanishi H, Ishii M, Kobayashi H. Necrotizing fasciitis caused by *Cryptococcus neoformans* in a patient with pemphigus vegetans. *Clin Exp Dermatol*. 2009;34:e751-e753.
5. Devaney B, Frawley G, Frawley L, Pilcher DV. Necrotising soft tissue infections: the effect of hyperbaric oxygen on mortality. *Anaesth Intensive Care*. 2015;43:685-692.
6. Zachariadou L, Stathi A, Tassios PT, et al; Hellenic Strep-Euro Study Group. Differences in the epidemiology between paediatric and adult invasive *Streptococcus pyogenes* infections. *Epidemiol Infect*. 2014;142:512-519.
7. Tancevski A, Bono K, Willis L, Klingele K. Necrotizing fasciitis in a pediatric orthopedic population. *Orthopedics*. 2013;36:e741-e745.

8. Danielsson PA, Fredriksson C, Huss FR. A novel concept for treating large necrotizing fasciitis wounds with bilayer dermal matrix, split-thickness skin grafts, and negative pressure wound therapy. *Wounds*. 2009;21:215-220.
9. Hodgins N, Damkat-Thomas L, Shamsian N, Yew P, Lewis H, Khan K. Analysis of the increasing prevalence of necrotising fasciitis referrals to a regional plastic surgery unit: a retrospective case series. *J Plast Reconstr Aesthet Surg*. 2015;68:304-311.
10. Hung CC, Chang SC, Lin SF, Fang CT, Chen YC, Hsieh WC. Clinical manifestations, microbiology and prognosis of 42 patients with necrotizing fasciitis. *J Formos Med Assoc*. 1996;95:917-922.
11. Nordqvist G, Walldén A, Brorson H, Tham J. Ten years of treating necrotizing fasciitis. *Infect Dis (Lond)*. 2015;47:319-325.
12. Edlich RF, Winters KL, Woodard CR, Britt LD, Long WB 3rd. Massive soft tissue infections: necrotizing fasciitis and purpura fulminans. *J Long Term Eff Med Implants*. 2005;15:57-65.
13. Testa A, Giannuzzi R, De Biasio V. Case report: role of bedside ultrasonography in early diagnosis of myonecrosis rapidly developed in deep soft tissue infections. *J Ultrasound*. 2015;19:217-221.
14. Maya SP, Beltrán DD, Lemercier P, Leiva-Salinas C. Necrotizing fasciitis: an urgent diagnosis. *Skeletal Radiol*. 2014;43:577-589.
15. Arif N, Yousfi S, Vinnard C. Deaths from necrotizing fasciitis in the United States, 2003-2013. *Epidemiol Infect*. 2016;144:1338-1344.
16. Tan JH, Koh BT, Hong CC, et al. A comparison of necrotising fasciitis in diabetics and non-diabetics: a review of 127 patients. *Bone Joint J*. 2016;98-B:1563-1568.
17. Park SJ, Kim DH, Choi CI, et al. Necrotizing soft tissue infection: analysis of the factors related to mortality in 30 cases of a single institution for 5 years. *Ann Surg Treat Res*. 2016;91:45-50.
18. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med*. 2004;32:1535-1541.
19. Sarkis P, Farran F, Khoury R, et al. Fournier's gangrene: a review of the recent literature [in French]. *Prog Urol*. 2009;19:75-84.
20. Bonnetblanc JM, Bedane C. Erysipelas: recognition and management. *Am J Clin Dermatol*. 2003;4:157-163.
21. Brogan TV, Nizet V, Waldhausen JH. Streptococcal skin infections. *N Engl J Med*. 1996;334:1478.
22. McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. *Ann Surg*. 1995;221:558-565.
23. Liu YM, Chi CY, Ho MW, et al. Microbiology and factors affecting mortality in necrotizing fasciitis. *J Microbiol Immunol Infect*. 2005;38:430-435.
24. Waldron C, Solon JG, O'Gorman J, Humphreys H, Burke JP, McNamara DA. Necrotizing fasciitis: the need for urgent surgical intervention and the impact of intravenous drug use. *Surgeon*. 2015;13:194-199.
25. Kotrappa KS, Bansal RS, Amin NM. Necrotizing fasciitis. *Am Fam Physician*. 1996;53:1691-1697.
26. Das DK, Baker MG, Venugopal K. Risk factors, microbiological findings and outcomes of necrotizing fasciitis in New Zealand: a retrospective chart review. *BMC Infect Dis*. 2012;12:348.
27. Altarac S, Katušin D, Crnica S, Papeš D, Rajković Z, Arslani N. Fournier's gangrene: etiology and outcome analysis of 41 patients. *Urol Int*. 2012;88:289-293.
28. el Benjelloun B, Souiki T, Yakla N, et al. Fournier's gangrene: our experience with 50 patients and analysis of factors affecting mortality. *World J Emerg Surg*. 2013;8:13.
29. Proud D, Raiola FB, Holden D, Paul E, Capstick R, Khoo A. Are we getting necrotizing soft tissue infections right? A 10-year review. *ANZ J Surg*. 2014;84:468-472.
30. Endorf FW, Klein MB, Mack CD, Jurkovich GJ, Rivara FP. Necrotizing soft-tissue infections: differences in patients treated at burn centers and non-burn centers. *J Burn Care Res*. 2008;29:933-938.
31. Bucca K, Spencer R, Orford N, Cattigan C, Athan E, McDonald A. Early diagnosis and treatment of necrotizing fasciitis can improve survival: an observational intensive care unit cohort study. *ANZ J Surg*. 2013;83:365-370.
32. Carbonetti F, Carusi V, Guidi M, David V. Necrotizing fasciitis: s comprehensive review [in Italian]. *Clin Ter*. 2015;166:e132-e139.
33. Christensen L, Evans H, Cundick D, McShane M, Penna K, Sadoff R. Necrotizing fasciitis: case presentation and literature review. *N Y State Dent J*. 2015;81:24-28.
34. Shaw JJ, Psoinos C, Emhoff TA, Shah SA, Santry HP. Not just full of hot air: hyperbaric oxygen therapy increases survival in cases of necrotizing soft tissue infections. *Surg Infect (Larchmt)*. 2014;15:328-335.
35. Shupak A, Shoshani O, Goldenberg I, Barzilai A, Moskuna R, Bursztein S. Necrotizing fasciitis: an indication for hyperbaric oxygenation therapy? *Surgery*. 1995;118:873-878.
36. Kumar S, O'Donnell ME, Khan K, Dunne G, Carey PD, Lee J. Successful treatment of perineal necrotising fasciitis and associated pubic bone osteomyelitis with the vacuum assisted closure system. *World J Surg Oncol*. 2008;6:67.
37. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fasciitis. *Front Surg*. 2014;1:36.
38. Song C. Hypertrophic scars and keloids in surgery: current concepts. *Ann Plast Surg*. 2014;73(suppl 1):S108-S118.
39. AbouIssa A, Mari W, Simman R. Clinical usage of an extracellular, collagen-rich matrix: a case series. *Wounds*. 2015;27:313-318.
40. Cervelli V, Brinci L, Spallone D, et al. The use of MatriDerm® and skin grafting in post-traumatic wounds. *Int Wound J*. 2011;8:400-405.
41. Lumenta DB, Kamolz LP, Frey M. Adult burn patients with more than 60% TBSA involved-Meek and other techniques to overcome restricted skin harvest availability—the Viennese concept. *J Burn Care Res*. 2009;30:231-242.
42. Philandrianos C, Andrac-Meyer L, Mordon S, et al. Comparison of five dermal substitutes in full-thickness skin wound healing in a porcine model. *Burns*. 2012;38:820-829.

43. Sheridan R, Hegarty MT, Tompkins R, Burke JF. Artificial skin in massive burns—results to ten years. *Eur J Plast Surg*. 1994;17:91-93.
44. Muangman P, Engrav LH, Heimbach DM, et al. Complex wound management utilizing an artificial dermal matrix. *Ann Plast Surg*. 2006;57:199-202.
45. Chen WY, Abatangelo G. Functions of hyaluronan in wound repair. *Wound Repair Regen*. 1999;7:79-89.
46. Vindigni V, Cortivo R, Iacobellis L, Abatangelo G, Zavan B. Hyaluronan benzyl ester as a scaffold for tissue engineering. *Int J Mol Sci*. 2009;10:2972-2985.
47. Park D, Kim Y, Kim H, et al. Hyaluronic acid promotes angiogenesis by inducing RHAMM-TGFβ receptor interaction via CD44-PKCδ. *Mol Cells*. 2012;33:563-574.
48. Benedetti L, Cortivo R, Berti T, et al. Biocompatibility and biodegradation of different hyaluronan derivatives (Hyaff) implanted in rats. *Biomaterials*. 1993;14:1154-1160.
49. Caravaggi C, Barbara A, Sganzaroli A, et al. Safety and efficacy of a dermal substitute in the coverage of cancellous bone after surgical debridement for severe diabetic foot ulceration. *EWMA J*. 2009;9:11-14.
50. Caravaggi C, Grigoletto MF, Scuderi N. Wound bed preparation with a dermal substitute (Hyalomatrix® PA) facilitates re-epithelialization and healing: results of a multicenter, prospective, observational study on complex chronic ulcers (the FAST study). *Wounds*. 2011;23:228-235.
51. Myers SR, Partha VN, Soranzo C, Price RD, Navsaria HA. Hyalomatrix: a temporary epidermal barrier, hyaluronan delivery, and neodermis induction system for keratinocyte stem cell therapy. *Tissue Eng*. 2007;13:2733-2741.
52. Onesti M, Fino P, Fioramonti P, Amorosi V, Scuderi N. Reconstruction after skin cancer excision through a dermal induction template: our experience. *Int Wound J*. 2016;13:198-203.
53. Onesti M, Fino P, Ponzo I, Ruggieri M, Scuderi N. Non-surgical treatment of deep wounds triggered by harmful physical and chemical agents: a successful combined use of collagenase and hyaluronic acid. *Int Wound J*. 2016:13-22-26.
54. Onesti MG, Carella S, Maruccia M, Ciotti M, Scuderi N. The use of hyalomatrix PA in the treatment of extravasation affecting premature neonates. *Plast Reconstr Surg*. 2012;129:219e-221e.
55. Vindigni V, Bassetto F, Abatangelo S, et al. Temporary coverage of a forehead defect following tumor resection with a hyaluronic acid biological dressing: a case report. *Ostomy Wound Manage*. 2011;57:56-60.
56. Wagstaff MJ, Caplash Y, Greenwood JE. Reconstruction of an anterior cervical necrotizing fasciitis defect using a biodegradable polyurethane dermal substitute. *Eplasty*. 2017;17:e3.