

Case Report

A Mosquito Bite with Devastating Complications in an Immunocompromised Patient

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Keywords

Aspergillus flavus · Hematopoietic stem cell transplantation · Mesh graft · Phlegmon · Very severe aplastic anemia

Abstract

Infectious complications such as invasive aspergillosis or infection with *Stenotrophomonas maltophilia* (SM) in immunocompromised patients are associated with a high mortality rate. Our report concerns a 40-year-old male newly diagnosed very severe aplastic anemia (vSAA) who in consequence of a mosquito bite was suffering from skin lesion and consecutive soft tissue phlegmon subsequent to the administration of antithymocyte globulin; a full-thickness autologous meshed skin graft successfully performed to cover skin ulcers after allogeneic stem cell transplantation (SCT). This unusual case illustrates the importance of appropriate diagnosis, anti-infective therapy and close interdisciplinary diagnostic algorithms to minimize side effects and the selection of resistant strains and to improve patients' outcome.

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Introduction

Aplastic anemia (AA) is characterized by destruction of hematopoietic cells by the immune system resulting in hypoplastic bone marrow and peripheral pancytopenia. AA is further classified based on the degree of granulocytopenia with impact on the severity of infectious complications and survival [1]. Although the infection-related mortality has decreased during recent years, especially *aspergillus* infections are still a major issue in patients suffering from very severe AA (vSAA) [2, 3]. Additionally, *Stenotrophomonas maltophilia* (SM) was the most frequently isolated gram-negative pathogen in AA [4]. SM is a ubiquitously present Gram-negative bacillus characterized as an opportunistic and perhaps a true pathogen. Especially in immunocompromised patients, it is associated with a poor prognosis and therapeutic outcome. Normally, clinical presentations include pneumonia, bacteremia and urinary tract infections [5, 6]. The infection rate of SM is rare but globally increasing, varying between countries, hospitals, and geographic regions [6]. Wound infections due to SM are rare; for example, over the course of one year only 2/70 patients tested positive for SM in a major tertiary care teaching hospital in Germany [7].

Here we describe a patient with vSAA who, subsequent to an initial administration of antithymocyte globulin, was bitten by a mosquito and then developed *Aspergillus flavus* pneumonia and a SM-infected skin lesion with rapid deterioration to a soft tissue phlegmon with deep skin ulcers, necrosis and associated bacteremia. Subsequently, to cover the lesion the patient received a full-thickness autologous meshed skin graft from the lower leg on day +54 after allogeneic hematopoietic stem cell transplantation (SCT). This case underlines the importance of an early and close interdisciplinary collaboration and the feasibility of allogeneic SCT even in patients with severe active infections.

Case Presentation

The 40-year-old male patient presented initially with multiple petechiae and ecchymosis on his legs, which had appeared during his summer holidays. Emergency blood count revealed pancytopenia and bone marrow biopsy proved aplasia; vSAA was diagnosed with neutrophils under 0.1/nL, platelets under 20/nL and reticulocytes 2 per mille. Immunosuppressive therapy with antithymocyte globulin (ATGAM®; Pfizer, days 1–4; 40 mg/kg, 3,400 mg daily) and cyclosporine A was initiated but did not improve the blood count. Subsequently, repeated admissions to hospital were necessary due to febrile neutropenia. Additionally, he developed pretibial erysipelas after a mosquito bite on day –66 before SCT. Despite the initiation of broad spectrum anti-infective therapy, his clinical condition deteriorated with increasing inflammation scores and fever. SM was detected in blood cultures and in drained pus gained from the pretibial ulcers (Fig. 1). In addition, computed tomography and microbiological workup of bronchoalveolar lavage revealed invasive *aspergillus flavus* and SM pneumonia. Based on resistogram (sensitivity towards ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole and tigecycline; despite inpatient intolerance towards trimethoprim/sulfamethoxazole), the anti-infective medication was modified, but therapy proved difficult, prolonged and required repeated modification of the antibiotic regime. The wounds (6 × 4 and 2 × 2 cm) had to be surgically revised repeatedly (in detail: incision and drainage on day –54; debridement of extensors tendon sheath and of muscles, negative wound pressure therapy on day –40; debridement and renewing of negative wound pressure therapy on days –33 and –28, finally debridement of muscles and resection of extensor hallucis longus muscles' tendon on day –23 before

SCT) and were initially treated with bandages changed daily and then with negative wound pressure therapy (for illustration see Fig. 1). Due to necrosis and initially exposed wound conditions, extensor hallucis longus muscles' tendon had to be resected and extensor tibialis anterior muscles' tendon atrophied resulting in a drop foot, which was treated with a peroneus orthosis. Over the following weeks and despite intensive wound management, no signs of wound healing occurred and amputation was discussed. In addition, the patient developed septic cardiomyopathy (ejection fraction 32%) with symptomatic congestive heart failure. Since his complex invasive infections (necrotizing deep skin ulcers, aspergillus pneumonia) were all caused by vSAA, the patient underwent a salvage allogeneic HSCT in October 2016, 6 months after diagnosis. The conditioning regimen consisted of cyclophosphamide (day –6 to –3 at doses of 300 mg/m², qd), fludarabine (day –6 to –3 at doses of 30 mg/m², qd), antithymocyte globulin (Thymoglobulin®; Genzyme, day –4 to –3; 3.75 mg/kg bodyweight [bwt], qd) and total body irradiation with 2 Gy on day 0. He received 1.01 × 10⁶ CD34+ bone marrow stem cells/kg bwt from an unrelated, male, human leukocyte antigen allele matched 10/10 donor. Prophylaxis of Graft-versus-host disease (GvHD) consisted of tacrolimus, starting on day –5, combined with methotrexate given at doses of 10 mg/m² on day +1 and 8 mg/m² on day +3 and +6. Engraftment of granulocytes and leukocytes occurred both on day +22 and of thrombocytes on day +33. G-CSF was administered daily from day +2 to day +17 to avoid prolonged neutropenia in the setting of very severe infectious complications. The anti-infective medication consisted of aciclovir, moxifloxacin, atovaquone, isavuconazol and amphotericin B.

Concerning the pretibial wounds, extensive surgical debridement was continued and of two 20 cm gentamycin mini chains were placed into the deep ulcers combined with debridement and renewing of negative pressure wound therapy on days +40 and +47. On day +54 after allogeneic SCT, autologous full-thickness meshed skin graft transplantation from his lower leg was performed in the absence of signs of acute GvHD (for results see Fig. 2).

Antifungal medication was continued for 1 year leaving post inflammatory residue in sectional images. Cardiomyopathy recovered and left ventricular ejection fraction improved up to 46%. On day +650 the patient is alive and doing well in complete remission of vSAA. The use of the orthosis and intensive physiotherapeutic therapy resulted in nearly unaffected mobility (almost unremarkable drop foot, compensation by discreet hyperflexion in hip joint while walking, only lateral toes can be lifted, active plantar flexion only up to 30 degrees and dorsiflexion to up to 10 degrees, nearly no active inversion and reduced eversion; muscle strength 4/5).

Discussion

As infections are still responsible for mortality in immunocompromised patients and trifles such as mosquito bites can lead into devastating complications, prophylactic antibiotic, antifungal and antiviral medication is routinely administered. However, the use of anti-infectives may have facilitated colonization with and acquisition of SM in our patient and may further promote selection of resistant strains [5, 8].

As in our case, the anti-infective therapy proved difficult and prolonged because of defects in cellular immune defense. Allogeneic SCT can restore hematopoiesis in patients suffering from vSAA and promote the cure of life-threatening infections. In a cohort of 65 patients with SAA and infection undergoing SCT, patients completely responding to anti-infective treatment had a 92.9% 3-year-survival-rate compared to 85.4% of patients with incomplete response.

Of note, in this study 5/65 patients suffered from SM infection of the lung or soft tissue and were classified as incomplete responders to anti-infective treatment. None of those patients suffered from SM bacteremia [9], the mortality rate of which is reported to be as high as 10–69% [5].

SM infections are not restricted to hospitalized patients only and exhibit intrinsic resistance to multiple antibiotics. Thus, synergistic antibiotic therapy is the key to minimize side effects, selection of resistant strains and to improve patients' outcome [5, 6]. Poor overall and failure-free survival rates were associated with invasive fungal infections and poor performance status pre-SCT in the transplanted SAA cohort [9]. Interestingly, co-infection with *aspergillus fumigatus* was associated with an odds ratio of 5.9 to possibly isolate SM (51% cases vs. 9% controls), independent of steroid use [8]. Whether co-infection with *aspergillus flavus*, as in our case, promotes SM infection can only be conjectured.

Finally, anti-infective treatment and close interdisciplinary wound care paved the way for performing SCT in our patient and helped to avoid the much-discussed option of amputation. The effective treatment of wound infection is essential for a successful engraftment of skin grafts [10]. In general, allografts are restricted to related donors, as allografts from cadaveric donors – commonly used in burn injuries – would contain additional alien cells [11]. However, autografts can be disadvantageous, as they can initiate inflammatory responses and acute rejection [12]. Based on its pathophysiology, chronic GvHD is the main cause of skin transplant failures [13, 14]. As split-thickness skin grafts contract more than full-thickness skin grafts, they should not be used for aesthetically or functionally important areas [10]. In general, femoral dermatome split-thickness skin grafts can be used to cover defects on lower thigh. Although the donor-site morbidity is minimal in proceeding this way, it would leave an exudative wound behind, creating a second portal of entry for pathogens. On the other hand, full-thickness skin grafts of that size must be harvested from the groin area, despite entailing risk of infection due to its proximity to the anal region [10]. Based on the patients' hypotrophic muscles in consequence of immobilization, relative excess skin on the patient's lower leg represented the best way to cover wound defects and to minimize infectious complications in cases of vSAA and SCT. Meshing and negative pressure wound therapy were used to optimize growths of skin graft by removing local inflammatory mediators, edema fluid and mechanotransduction [10]. The discussed patient had an excellent skin engraftment with satisfactory functional and cosmetic result, as shown in Figure 2.

Taken together, pinpoint antibiotic therapy and disciplined wound management is crucial for successful treatment of SM infections in immunocompromised patients. Furthermore, salvage allogeneic SCT is feasible in young patients with severe active co-infections and good performance status before SCT [15]. Close interdisciplinary diagnostic algorithms and cooperation are indispensable. To the best of our knowledge, this is the first report of a skin autograft to cover wound defects performed less than two months after allogeneic SCT in vSAA.

Acknowledgement

Not applicable.

Statement of Ethics

The authors have no ethical conflicts to disclose. Written informed consent was obtained from our patient for publication of this case report. A copy of written consent is available for review.

Disclosure Statement

The authors do not declare any conflicts of interest.

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Author Contributions

All authors read and approved the final manuscript. NW, SS, US FH and FJH collected and provided data on the inpatient and outpatient treatment of the case presented. TD, FG and ML performed surgical procedures und managed wound control. JF and IH analyzed data, compiled diagnostic data and wrote the manuscript.

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Fig. 1. Intraoperative situs: **A:** about 5 × 6 cm and further distal 3 × 2 cm covering defect with exposed atrophic tend; **B:** surgical cleaning; **C:** deposition of gentamycin mini chains; **D:** negative pressure wound therapy.



Fig. 2. Postoperative results: **A:** 9 days; and **B:** 20 months after surgical intervention.