



'Lost in Nasal Space': *Staphylococcus aureus* sepsis associated with Nasal Handkerchief Packing

Philipp Koehler^{1,2} · Norma Jung¹ · Matthias Kochanek¹ · Philipp Lohneis³ · Alexander Shimabukuro-Vornhagen¹ · Boris Böll¹

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Abstract

Introduction *Staphylococcus aureus* frequently causes infections in outpatient and hospital settings and can present as a highly variable entity. Typical manifestations are endocarditis, osteoarticular infections or infection of implanted prostheses, intravascular devices or foreign bodies. A thorough diagnostic evaluation with early focus identification is mandatory to improve patient outcome.

Case report We report a case of a 68-year old patient with a history of double allogeneic stem cell transplant for acute myeloid leukemia who developed a *S. aureus* bacteremia with dissemination, severe sepsis and lethal outcome due to nasal handkerchief packing after nose bleeding.

Conclusion A thorough medical examination with further diagnostic work-up is most important in *S. aureus* blood stream infection to identify and eradicate the portal(s) of entry, to rule out endocarditis, to search for spinal abscesses, osteomyelitis or spondylodiscitis. Adherence to management guides for clinicians must be of major importance to achieve optimal quality of clinical care, and thus improve patient outcome.

Keywords Dissemination · Superantigen · Intensive care medicine · Infectious disease consulting

Introduction

Staphylococcus aureus is a human and animal commensal and frequently identified as pathogen causing infections [1, 2]. *Staphylococcus aureus* colonizes the skin, mucosae and typically the anterior nares of the nose [2]. *Staphylococcus aureus* nasal carriage varies between different ethnic groups with higher rates in Caucasians [3], men [4, 5], and shows different rates due to age (declining colonization in infants

with increasing age) [6, 7]. *Staphylococcus aureus* carriage is co-determined by host characteristics (e.g. inherent resistance to colonization or occupied rhinal niche by other bacteria) [8] and hands are the major vector for the transmission of *S. aureus* to the nose [9].

Staphylococcus aureus bacteremia is one of the most frequent bacterial infection throughout the world and its clinical presentation can be highly variable. Typical manifestations are endocarditis, osteoarticular infections (spondylodiscitis, osteomyelitis, or joint infections), infection of implanted prostheses, intravascular devices/foreign bodies, septic thrombophlebitis, and or visceral abscesses [10].

For patients with *S. aureus* bacteremia mortality of 20–40% are reported in the literature [11, 12]. In patients, where the focus cannot be established, a substantially higher day 90-mortality is reported in comparison to patients with identified focus [13]. *Staphylococcus aureus* exotoxins, especially the toxic shock syndrome toxin-1 (TSST-1) lead to shock, erythroderma and multiorgan failure due to their ability of simultaneously activating a large number of T cells (superantigen) leading to massive cytokine release.

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✉ Boris Böll
boris.boell@uk-koeln.de

- ¹ Department I of Internal Medicine, Intensive Care Unit, University Hospital of Cologne, Cologne, Germany
- ² Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
- ³ Institute of Pathology, University Hospital Cologne, Cologne, Germany

Here, we describe the case of a 68-year-old man who presented to our department with a livid discoloration of his nose, an increasing dyspnea and malaise due to a severe disseminated *S. aureus* bacteremia with consecutive sepsis triggered by nasal handkerchief packing with lethal outcome.

Case presentation

A 68-year old man presented to the emergency department because of increasing dyspnea and malaise, decreased vigilance and a livid discoloration of his nose with partly necrotizing tissue and swelling of his face, which had started the week before his presentation (Fig. 1). The patient reported a history of two allogeneic stem cell transplantations (aSCT) for acute myeloid leukemia (AML) (Cytogenetics: 46 XY, complex aberrant karyotype, TP53-deletion, NF1-deletion; molecular characterization: high WT1 expression, NPM1/MLL/FLT3/IDH1: negative) He had received the first aSCT at the age of 65 (MUD 10/10). He had undergone a second aSCT 1 year prior to admission (MUD 10/10) because of relapse of AML 30 months after the first aSCT. Prior to the second aSCT, an acute kidney disease was diagnosed due to compression of the ureters by granulocytic sarcomas (so called chloromas). The last change of double J stents was performed 7 days prior to admission to the clinic.

Ten days prior to his hospitalization the patient presented to the outpatient clinic of the bone marrow transplant unit due to increasing polyserositis and oral steroids with 100 mg daily were administered for 4 days. Polyserositis was leading symptom of his chronic graft-versus-host disease (GvHD) with recurring pleural effusion and

ascites, but he was otherwise in good general condition and capable of all self-care with assistance of his wife. Due to recurrent thrombocytopenia after aSCT the patient received repetitive thrombocyte transfusions and his wife described long lasting nose bleeds in the last days prior to admission to the hospital.

On examination, the patient appeared in bad general condition. The temperature was 38.7 °C, the heartrate 120 beats per minute, the blood pressure 110/63 mmHg, the respiratory rate 43 breaths per minute, and the oxygen saturation 96% while breathing 4 L oxygen (85% on ambient air).

Examination of the legs showed bilateral edema of the lower extremities, ascites and bilateral pleural effusions. Examination of the skin revealed a livid discoloration of his nose, open-grained and in parts with necrotizing tissue (Fig. 1a).

Laboratory examination revealed high C-reactive protein levels of 308.7 mg/L (2940.06 nmol/L), procalcitonin levels of 5.1 µg/L and white blood cell count of $2.17 \times 10^9/L$ (2170/µL). At presentation in the emergency room an empiric antibiotic therapy was initiated intravenously with ceftriaxone (2 g every day) and clarithromycin (500 mg, twice a day) after collection of blood cultures, which then was empirically switched to piperacillin/tazobactam (4,5 g, three times a day) at admission to the intensive care unit (ICU) after 1 day due to initially suspected community-acquired pneumonia in a highly immunosuppressed patient.

Reasons for admission to ICU were septic shock and decompensated heart and renal failure with edema, pleural effusion and ascites. Diuretics and vasopressor support were initiated and computed tomography of the cranium, chest and abdomen was performed. It showed destruction and swelling of the rhinal cartilages at the distal end and at the

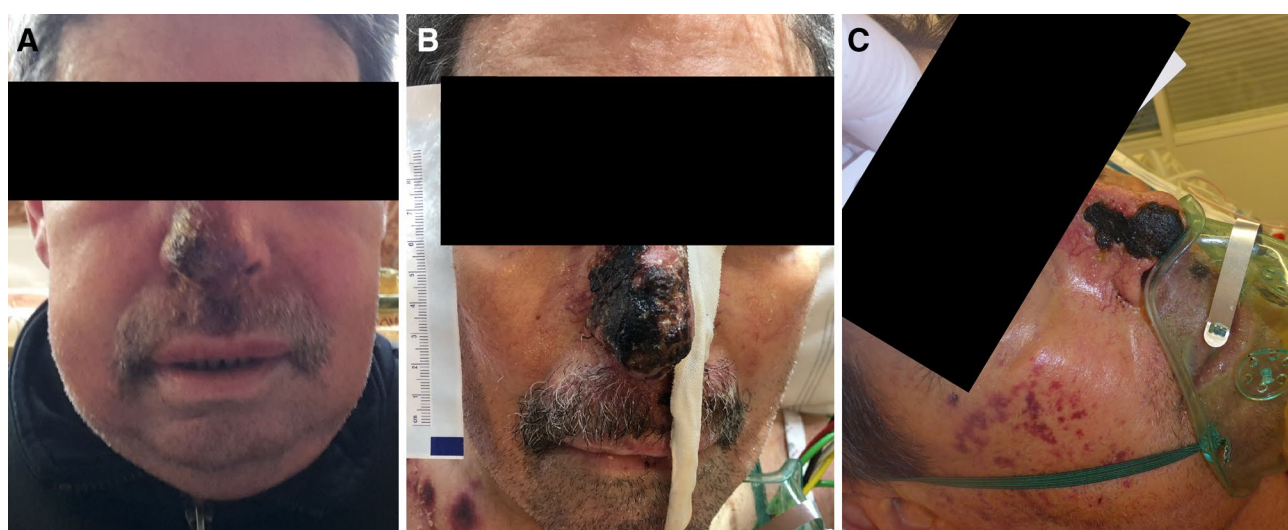


Fig. 1 Clinical image of skin and soft tissue due to *S. aureus*. **a** Day 0—admission to emergency room; **b** day 11; **c** day 24 after admission, 3 days prior to death of the patient

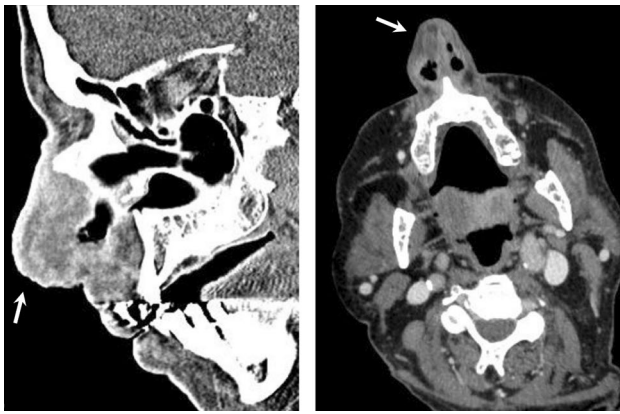


Fig. 2 Cranial Computed Tomography at Day 3. Arrows show destruction and swelling of the rhinal cartilages at the distal end and at the alae of the nose without signs of bone affection

alae of the nose without signs of bone affection (Fig. 2). Furthermore, an increasing facial soft tissue swelling without signs of sinusitis was found. Due to the livid discoloration of the nose with necrotizing tissue, increasing dyspnea and septic shock we immediately performed a nasal endoscopy to take biopsies for microbiological and histopathological work-up. During endoscopy, small pieces of a handkerchief were extracted from the nasal cavity. Upon questioning, the patient's wife confirmed that a handkerchief was placed by the patient about 10 days prior to admission for nasal packing to reduce the nose bleeding. Upon cessation of nose bleeding, the patient had forgotten the handkerchief, resulting in a foreign body in the nasal cavity.

Microbiological and histopathological diagnostics showed signs of deep tissue infiltration of bacteria with necrotizing tissue adjacent without signs of tumor or fungal hyphae (Figure S1). *Herpes simplex* infection was ruled out by negative PCRs from full blood and negative local swab from the necrotizing tissue at the nose. Culture of the tissue biopsy revealed methicillin-susceptible *Staphylococcus aureus* (MSSA). Cultured urine, blood and ascites grew methicillin-susceptible *S. aureus* repeatedly.

With the result of MSSA growth in culture flucloxacillin (2 g, three times a day, dose adjusted because of renal failure) was added on day 2 and indwelling intravascular catheters and ureteral double J stents were changed. A transesophageal echocardiogram did not show any sign of endocarditis. With progressive hypotension despite fluid therapy and encephalopathy, with disorientation, confusion, and reduced vigilance a lumbar puncture was performed to rule out MSSA meningitis. During the antibiotic therapy with flucloxacillin blood cultures did not reveal growth of *S. aureus* again, however, vancomycin-resistant *Enterococcus faecium* on day 5 (VRE), linezolid was added and indwelling catheters were changed again. Due to suspected

calcineurin inhibitor toxicity indicated by an increase of schistocytes to 10% tacrolimus was stopped and Prednisolone (2 mg/kg body weight) was administered as bridge immunosuppression therapy. At day 12 tracheal intubation was needed due to further respiratory deterioration. Due to sustaining anuria a slow low-efficient daily dialysis (SLEDD) was started. At day 17 blast cells were detected in ascites and peripheral blood with increasing expression of the Wilms tumor 1 gene (WT1). Chimerism analysis showed complete engraftment of the bone marrow transplant consistent with extramedullary relapse of AML. Due to hematemesis and melena an upper endoscopy showed a necrotizing esophagitis with gastric ulcers and a diffuse oozing hemorrhage. By means of proton pump inhibitors and platelet transfusions the hemorrhage remained stable. Full blood testing showed a reactivation of *Cytomegalovirus* (CMV), so that a therapy with ganciclovir was initiated. With recovery of the neurological state the patient was extubated on day 21. 5 days later the general state of health deteriorated rapidly. The patient remained febrile, inflammation parameters increased without relapse of *S. aureus* bacteremia. The patient developed respiratory insufficiency, hypotension and reduced vigilance. In light of the long medical history with progressive leukemia, we discussed the situation in-depth with the patient's family and agreed to change the main goal of treatment to best supportive care. The patient died of progressive leukemia after severe disseminated *S. aureus* bacteremia on day 27.

Discussion

We report an unusual case of a patient with severe disseminated *S. aureus* bacteremia associated with nasal handkerchief packing. Our patient developed septic shock with fever, rash, hypotension, multisystem involvement combined with disseminated cultural evidence of *S. aureus* in blood cultures, ascites, urine, and in the nasal biopsy.

Staphylococcus aureus bacteremia must always be considered clinically relevant, carrying increasing risk of dissemination with metastatic seeding and complications [14]. Once diagnosis of *S. aureus* bacteremia is established, repeated blood cultures for the documentation of clearance should be drawn, as length of bacteremia and fever is critical for further diagnostic work-up, for the duration of antibiotic therapy and prognosis. Key predictors for complicated *S. aureus* bloodstream infection are community acquired infection, skin examination findings suggesting acute systemic infection (petechiae, vasculitis, infarcts, echymoses or pustules), persistent fever at 72 h, and positive follow-up blood culture results at 48–96 h [15].

In our patient, we initially established a sufficient antibiotic therapy empirically with piperacillin/tazobactam due

to the suspicion of community acquired pneumoniae in a immunosuppressed patient and added flucloxacillin with the cultural proof of *S. aureus* bacteremia. Following blood cultures after the extraction of the handkerchief, changing of indwelling catheters and double J stents during antibiotic therapy remained negative for *S. aureus*, after a 27 day course of therapy. We did not add clindamycin (only in vitro data for TSST-1 synthesis suppression), intravenous immune globulin (IVIG) or corticosteroids initially due to limited clinical data. An acceptable and well-tolerated alternative for treatment of methicillin-susceptible *S. aureus* is cefazolin (2 g iv every 8 h) [16–18].

Asking for and understanding the patient's medical history and a thorough medical examination with further diagnostic work-up is most important to identify and eradicate the portal(s) of entry, to rule out endocarditis, to search for spinal abscesses, osteomyelitis or spondylodiscitis. Repetitive bedside examinations can reveal the development of complications that may evolve in the course of infection (e.g. metastatic seeding). Infectious disease consulting at the bedside is a major component of management of patients with *S. aureus* sepsis and should be asked for whenever feasible [19].

Due to rising age of population, increasing case severity, and growing number of patients with immunosuppression *S. aureus* associated skin and soft tissue infections with consecutive blood stream infection put patients at a high risk and adherence to management guides for clinicians must be of major importance to achieve optimal quality of clinical care, and thus improve patient outcome [10, 20].

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Compliance with ethical standards

Conflict of interest PK reports non-financial support from Merck/MSD, non-financial support from MedImmune, and lecture honoraria from Astellas outside the submitted work. NJ received lecture fees from Labor Stein, Novartis, Gilead, MSD, Infectopharm and travel grants from Novartis, Pfizer, Astellas, Basilea, Gilead. MK declares no potential conflict of interest in regard to this work. PL declares no potential conflict of interest in regard to this work. ASV declares no potential conflict of interest in regard to this work. BB declares no potential conflict of interest in regard to this work.

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