Title

Persistent Methicillin-Resistant *Staphylococcus aureus* Bacteremia in an Adult Patient with Netherton's Syndrome: A Case Report

Authors

Misa Takahashi[a], Hideharu Hagiya[a]*, Shuichi Tanaka[a], Koichiro Yamamoto[a], Hiroyuki Honda[a], Kou Hasegawa[a], Fumio Otsuka[a]

[a]Department of General Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700-8558, Japan

E-mail address:

Misa Takahashi (misataka1215@s.okayama-u.ac.jp), Hideharu Hagiya (hagiya@okayama-u.ac.jp), Syuichi Tanaka (pbmc7rcx@s.okayama-u.ac.jp), Koichiro Yamamoto (pi291nd8@s.okayama-u.ac.jp), Hiroyuki Honda (ppgf1hrd@okayama-u.ac.jp), Kou Hasegawa (khasegawa@okayama-u.ac.jp), Fumio Otsuka (fumiotsu@md.okayama-u.ac.jp)

***Corresponding author**

Hideharu Hagiya, M.D., Ph.D., CTH, CIC

Department of General Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.

Tel: +81-86-235-7342 Fax: +81-86-235-7345

E-mail: hagiya@okayama-u.ac.jp

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[1] Abbreviations used in the manuscript

[1] MRSA, methicillin-resistant *Staphylococcus aureus*; PICC, peripherally inserted central venous catheter; CA-MRSA, community-acquired MRSA

Abstract

Netherton's syndrome, a rare congenital disorder, is clinically characterized by chronic dermatologic disorders such as ichthyosiform erythroderma and ichthyosis linearis circumflexa. Curable treatment is yet to be established, and corticosteroid ointment is required to maintain good dermatological condition. Because of the permanent skin barrier impairment, patients with Netherton's syndrome are considered to be vulnerable to cutaneous infections. However, its clinical characteristics are yet to be elucidated due to the limited number of reported cases. Herein, we describe the clinical course of a patient who developed persistent methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. A 19-year-old Japanese woman who had been diagnosed with Netherton's syndrome in her infancy and had been applying topical corticosteroid agents all over her body since her then, was referred to our hospital because of persistent MRSA bacteremia and secondary adrenal insufficiency. The patient was diagnosed with a central line-associated bloodstream infection and was appropriately treated with antibiotics and corticosteroid therapies. We assume that the damaged skin barrier due to the congenital dermatological disorder causes a disruption in the normal bacterial flora of the skin, leading to the invasion of harmful bacteria, such as *S. aureus*. In addition, internal (humoral immunodeficiency by decreased antibody against bacterial polysaccharide

antigens) and external (prolonged and systemic use of corticosteroid ointment) factors bring about an immunodeficiency state in such patients. We highlight that in the absence of radical treatment, clinicians need to recognize that patients with Netherton's syndrome are vulnerable to bacterial infections owing to the mixture of immunosuppressive factors.

Keywords: Netherton’s syndrome; MRSA; bacteremia; central line associated bloodstream infection; corticosteroid.

Introduction

Netherton's syndrome is a rare, chromosomally-recessive genetic disease, which involves 1 in 200,000 newborns [1]. In most cases, patients present with systemic erythroderma (red, scaly skin) at birth, specifically characterized by congenital ichthyosiform erythroderma, ichthyosis linearis circumflexa, hair shaft abnormalities, and atopic disease with an elevation of serum IgE level [2, 3]. The disease is caused by mutations in the serine peptidase inhibitor kazal-type 5 gene, which encodes the lymphoepithelial kazal-type-related inhibitor protein [2]. Because of impaired skin barrier due to LEKT1 deficiency [4], patients are vulnerable to repeated bacterial infections and dehydration; thus, they are at a high risk of mortality and morbidity in infancy [5]. The skin condition usually improves with age, and adult patients may merely present localized patches of redness and scaling or ichthyosis linearis circumflexa [4]. Erythroderma persists in some patients and develops into circumferential linear ichthyosis in others, which is often complicated by skin infections. These patients have a chronic recurrent course with cutaneous symptoms, generalized pruritus (itching), and pain. Symptomatic treatment with corticosteroid ointment is currently the only available therapy, although new therapeutic strategies are being developed, such as intravenous immunoglobulins [5], anti-tumor necrosis factor alpha agents [6], and dupilumab [7]. Herein, we describe a case

of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia that involved an adult patient with Netherton's syndrome.

Case Report

A 19-year-old Japanese woman with Netherton's syndrome, as a congenital underling disease, presented to her previous doctor with a sudden-onset of high fever and general malaise. She had a systemic ichthyosiform erythroderma, for which she had been applying topical betamethasone (very strong) to the whole body since early childhood. Upon admission, she was diagnosed with urinary stone pyelonephritis caused by *Streptococcus agalactiae*, for which she was started on piperacillin/tazobactam 4.5 g every 8 hours. To intravenously administer the antibiotic, a peripherally inserted central venous catheter (PICC) was inserted due to difficulty in accessing a peripheral vein. The patient underwent 14 days of antibiotic therapy and was discharged.

However, after 5 days she again developed high fever and was re-admitted to the hospital with a re-insertion of the PICC. At the re-admission, she had erythroderma to the whole body. Especially she had severe erythema on the face and head with flacking and hair shaft defect. Blood drawn for culture on day 5 of the re-admission was positive for MRSA, and intravenous vancomycin 1 g every 12 hours was initiated. On day 11,

abdominal pain, malaise, and hypoglycemia appeared, and serum levels of adrenocorticotropic hormone 7.5 pg/mL and cortisol 2.4 μg/dL were found to be decreased. A diagnosis of secondary adrenal insufficiency was made in the patient, and an intravenous infusion of hydrocortisone 200 mg/day was promptly started, which was subsequently tapered to the oral form of hydrocortisone 90 mg/day. Blood culture on day 16 was again positive for MRSA accompanying *Acinetobacter baumannii* complex, and the patient was transferred to our institute because of the complicated clinical course. The detected MRSA was resistant to β-lactam, clindamycin, and gentamicin but susceptible to minocycline and levofloxacin.

Upon hospitalization, she had a body temperature of 37.6 °C, blood pressure of 120/76 mmHg, pulse rate of 83/minute, oxygen saturation of 99% at room air, and a respiratory rate of 18/minute. Physical examination revealed no abnormalities in her heart, lungs, and abdomen. Her face and extremities were generally edematous with ichthyosiform erythroderma (**Fig. 1 A, B**). There was a local tenderness and swelling on her right upper arm where the PICC was inserted at the previous hospital. Peripheral embolic lesions, such as petechiae under the nails, Janeway lesion on the palms and soles, and spot bleeding at the eyelid conjunctiva were absent. Laboratory data showed an increase in white blood cells (14,700/μL) and elevated serum levels of C-reactive protein

(30.1 mg/dL) and procalcitonin (46.4 ng/mL). Serum levels of immunoglobulins and complements were as follows; IgG 801.7 mg/dL, IgA 140 mg/dL, IgM 79.1 mg/dL, IgE 1,114 IU/mL, C3 102.5 mg/dL, C4 25.4 mg/dL. Of note, serum IgG level decreased below a normal range (861–1747 mg/dL), while IgE exceeded a normal value (<170 IU/mL). Cardiac ultrasonography detected no lesion suggesting endocarditis. Contrast-enhanced computed tomography detected no pulmonary emboli or abscess formation, while bilateral reactive lymph node enlargements in the axillae and groin were observed. During the hospitalization, we changed the topical betamethasone to hydrocortisone butyrate (medium). We removed the PICC insertion, and a combination of daptomycin 350 mg every 24 hours and ceftazidime 1 g every 8 hours was started, after which her condition improved, and follow-up blood culture examinations remained negative. Under the diagnosis of central line-associated bloodstream infection, the patient completed 2 weeks of antibiotic treatment and was discharged. At this point, her edematous, erythroderma appearance ameliorated (**Fig. 1C, D)**.

Discussion

We described a patient with Netherton's syndrome who developed MRSA-induced bloodstream infection. In addition to skin barrier disruption, a combination of internal

and external immunosuppressive factors predisposes such patients to various bacterial infections. However, our literature review did not find any similar cases reporting an adult patient with Netherton's syndrome suffering from MRSA bacteremia. Because of this, we consider this clinical report to be valuable in the literature.

Chronic dermatological disruption is the primary cause of bacterial infections in patients with Netherton's syndrome. Majority of the patients have atopic dermatitis characterized by the following conditions: (1) abnormal skin barrier function; (2) cutaneous immune abnormality predisposed to T-helper 2 immunity; and (3) decreased diversity of bacterial flora on the skin surface [8, 9]. A decrease in microbiome diversity correlates with disease severity and increased colonization with pathogenic bacteria, such as *S. aureus* [9, 10]. Thus, patients with atopic dermatitis are disposed to cutaneous and consequently systemic bacterial infections. In fact, chronic skin diseases such as atopic dermatitis and psoriasis increase the risk of bacterial infections including *S. aureus* [11, 12]. In addition to the skin impairment, other internal and external factors bring about a state of immunodeficiency in patients with Netherton's syndrome. For example, the number of natural killer cells remains normal, but their function is reported to be impaired [5]. It has also been uncovered that these patients have a selective antibody deficiency against bacterial polysaccharide antigens [13]. Practically, patients with Netherton's

syndrome have increased rates of respiratory and gastrointestinal infections as well, and immunoglobulin replacement therapy can reduce episodes of such bacterial infections [5]. Moreover, the long-term exposure to topical corticosteroid for the purpose of controlling the ichthyosis condition inevitably provokes a steroid-induced cellular immunodeficiency [3, 14]. Thus, we should clinically regard patients with Netherton's syndrome as immunocompromised patients.

With the antimicrobial susceptibility pattern, we assume that the MRSA strain isolated from the patient can be classified into community-acquired MRSA (CA-MRSA). It mostly remains susceptibility to various antibiotics but possesses multiple virulence factors compared to conventional, hospital-acquired MRSA strains [15]. The isolation rate of CA-MRSA is particularly higher in the field of dermatology [15, 16, 17, 18], but it potentially yields systemic involvement by causing disseminated infections [19]. Although a secondary infectious focus was not evident in this case, a systemic examination is recommended when CA-MRSA is suspected.

In summary, we illustrated a case of MRSA bacteremia involving an adult patient with Netherton's syndrome. Patients with this genetic disease are vulnerable to bacterial infections due to the complicated mixture of immunodeficient factors, including skin barrier disorder, humoral immunity dysfunction, and long-term exposure to corticosteroid

agents.

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Figure Legend

Figure 1. Dermatologic appearance of the present patient with Netherton's syndrome

A to D: Upon transfer to our hospital; Ichthyosiform erythroderma is observed on her face and extremities. E to H: Just before the discharge; Ichthyosiform erythroderma ameliorated but ichthyosis remains.