

## Case Report

# Successful treatment of enterococcus faecium sepsis and meningitis by intravenous and intrathecal vancomycin in children with Wiskott-Aldrich syndrome undergoing cord blood transplantation: a case report

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**Abstract:** Infectious disease is common in stem cell transplant recipients, especially in the patients of primary immunodeficiency disease (PID). However, there's little report about sepsis and meningitis caused by enterococcus faecium (EF). Meningitis and sepsis caused by EF is uncommon in stem cell transplant recipients. We report a case of EF meningitis and sepsis which occurred in a 2-year-old boy with Wiskott-Aldrich syndrome (WAS) and received cord blood cell transplantation (CBT). After our therapy, he got a good result and completely remission by combination therapy of intravenous and intrathecal vancomycin. We believe it is the first case of EF infection in WAS patient following CBT.

**Keywords:** Enterococcus faecium, sepsis, meningitis, Wiskott-Aldrich syndrome, vancomycin, cord blood transplantation

## Introduction

Infectious disease is common in stem cell transplant recipients [1], especially in the patients of primary immunodeficiency disease (PID). However, there's little report about sepsis and meningitis caused by Enterococcus faecium (EF), which is difficult to managed such condition because it is difficult to get an effective drugs level, such as vancomycin and linezolid, in cerebrospinal fluid (CSF) [2]. There were several studies about combination therapy of intravenous and intrathecal vancomycin for meningitis [3]. However, there had no report about such therapy in PID patient who received stem cell transplantation according to our knowledge. In this study, we described a 2-year-old boy who suffered from Wiskott-Aldrich syndrome (WAS), which is a common kind of PIDs. He received allogeneic cord blood transplantation (CBT) therapy, and occurred meningitis and sepsis caused by EF. After our therapy, he got a good result and completely remission by combi-

nation therapy of intravenous and intrathecal vancomycin.

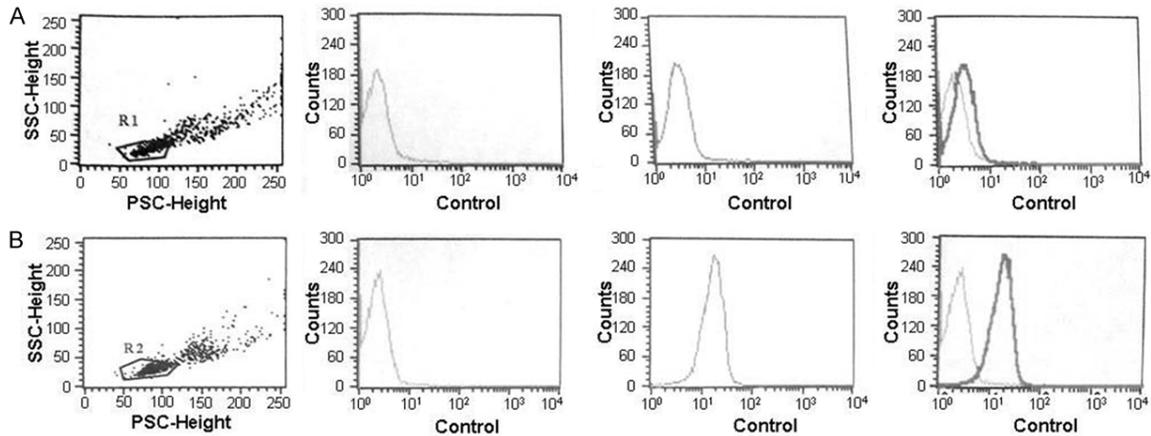
## Case report

### Case description

A 2-year-8-month-old boy presented with recurrent infection, eczema, bleeding and thrombocytopenia after birth. Recurrent and refractory infectious disease included upper respiratory tract infection, bronchitis, pneumonia and diarrhea. Eczema occurred in unusual sites which included belly, legs and arms. Bleeding induced by thrombocytopenia and presented with purpura, petechiae, trace of blood in his stool. No apparent physical exams were found except petechiae.

In the present study, the patient received cord blood cell transplantation (CBT). The method of the CBT was performed according to the previous study [4]. The child underwent a routine

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**Figure 1.** Flow cytometry examination for allogeneic cord blood transplantation treatment for the patient. A. Before allogeneic cord blood transplantation treatment. B. After allogeneic cord blood transplantation treatment.

complete blood count with differential count. The present study was approved by the ethics committee of Children's Hospital of Chongqing Medical University, Chongqing, China. The child's mother has also approved this study and gave her consents. Venous blood samples for complete blood cell counts were analyzed according to laboratory practice using an STK-S counter (Coulter Corporation, Haileah, FL, USA). Differential cell counts were performed manually, and nucleated RBC counts were counted per 100 WBC. The white blood cell counts (WBCC) was determined using an Abbott Cell Dyn 3000 hematology analyzer (Abbott Laboratories, Abbott Park, Illinois, USA).

IgA, IgG, IgM and IgE were measured by using commercial ELISA kits (Sigma-Aldrich, CA, USA) according to the manufacturer's instructions. When received in the hospital, the level of IgG was 5.09 g/L, IgA was 0.31 g/L, IgM was 0.4 g/L, and IgE was less than 150 U/L.

The blood cells were aliquoted and stained with anti-CD3<sup>+</sup>, CD4<sup>+</sup>, CD8<sup>+</sup>, CD19<sup>+</sup>, CD56<sup>+</sup> or isotype controls at 4°C for 30 minutes. The cells were then washed twice with phosphate buffered saline (PBS). After fixation and permeabilization, the cells were analyzed on a flow cytometry (BD Biosciences FACS Aria, CA, USA).

Also, the WASP was encouraged to examine non-transplanted patients for somatic mosaicism in peripheral blood cells by flow cytometry [5]. The patient and his mother received genetic analysis by PCR sequencing. The result showed that there is a deletion in No. 36 codon

for exon I, which means TTT was transferred to TGA, and also means that the UUU (Phe, F) was transferred to UGA (Stop). Therefore, the boy was identified as WAS patient, and his mother was a carrier.

### *The case therapeutic outcome*

Completely blood count (CBC) showed PLT level was  $2 \times 10^9/L$ , WBC level was  $0.03 \times 10^9/L$ . The absolute neutrophil count (ANC) was  $0.5 \times 10^9/L$ . After the treatment with the CBT, the PLT even achieved to more than  $100 \times 10^9/L$ , and WBC achieved to  $22 \times 10^9/L$ . The transplanation time and processes for the CBT were performed according the previous study [4]. The absolute neutrophil count (ANC) even more than  $1.5 \times 10^9/L$  after the treatment with CBT.

After treatment with the CBT, all of the proteins, including IgG, IgA, IgM, IgE achieve to the normal level.

The flow cytometry (FCM) examination for lymphocytes indicated that CD3<sup>+</sup> achieved to 39%, CD19<sup>+</sup> to 21%, CD4<sup>+</sup> to 26%, CD8<sup>+</sup> to 10%, and CD56<sup>+</sup>16<sup>+</sup> to 38%. Furthermore, the ratio for CD4<sup>+</sup> and CD8<sup>+</sup> was 2.60%. After treatment with CBT, all of the above CDs achieved to the normal differentiation.

The FCM assay was employed to examine the level of WASP. Before treatment, the there was a negative expression for WASP protein (**Figure 1A**). After treatment with vancomycin, the WASP protein was positively expressed in the patient (**Figure 1B**).

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After treating with the CBT, the patient underwent the EF infection, and the vancomycin was used to treat the EF infection. No obvious adverse events related to vancomycin were noted during the treatment. EF infection did not recur and the boy got completely remission. With 5 years following-up, he lives without recurrent infection and thrombocytopenia. Immunological analysis was tested yearly and these results were normal. WASP protein was also examined, and no positive expression.

### Discussion

Wiskott-Aldrich syndrome is an X-linked recessive PID which was firstly described by Wiskott and Aldrich in 1937 and 1954 respectively [5]. In clinical, it features as refractory and recurrent infections which usually occur in respiratory, urine or digestive tract, bleeding due to thrombocytopenia and atopic eczema that usually occurs in trunks or extremities [6]. Affected males usually died before 20 years old because of infection, fetal hemorrhage or neoplasm [7]. Morbidity was reported to not be less than 4 per 10,000,000 in USA and Canada [8]. Its genetic defect has been illustrated to Xp 11.2 region, and carrier detection with the hypervariable M27- $\beta$  probe is now feasible [9].

The genetic origin of WAS in this case is showed deletion in No. 36 codon for exon I, which means TTT was transferred to TGA, that was UUU (Phe, F) transferred to UGA (Stop), the normal WAS gene may encode 502 amino acid but it encodes only 35 amino acid now. The affected boy's mother was a female carrier and was detected same mutated gene which had been reported before [10].

The outcome of untreated WAS patients is poor and lacks of any other curative way. Stem cell transplantation from matched related donor may reconstitute the damaged immune functions and thrombocytopenia, so does from unrelated donor [11-13]. In this case, the boy received 4/6 matched cord blood transplantation. He got complete hematology and immunology recovery. It is now 5 years since transplantation, clinically, our patient's eczema has resolved. He is free from frequent infections and has good growth and development because of normal immunologic function. He has no bleeding tendency because of normal platelet counts.

*Enterococcus faecium* is a Gram-positive bacillus that is widespread in nature. In the human gastrointestinal tract (GIT), EF is the most common strains. In foods of animal origin (cheese, pork meat, beef, poultry meat), EF is also very frequent [14]. EF is resistance to many antimicrobial agents, and even vancomycin resistant enterococci (VRE) have been isolated [15]. In this case, the boy was suffered from diarrhea induced by GVHD in GIT, species for stool, blood and CSF is positive to EF. We regard that the bacterium was transferred from GIT to blood and sepsis occurred, then meningitis was induced for sepsis. Sepsis caused by EF could be cured by intravenous vancomycin if bacterium are sensitive to it [15]. But in cases of meningitis caused by EF, disease is hard to be cured because it is not easy to get satisfied serum vancomycin level in cerebrospinal fluid (CSF) [3]. Vancomycin is one of the glycopeptides narrow spectrum antibiotics produced by *Streptomyces Orientalis* [15]. It was for the treatment of infections caused by Gram-positive bacteria. However, early clinical reports noted a high incidence of nephrotoxicity and neurotoxicity associated with vancomycin, it was abandoned and replaced by other less toxic antibiotics, such as beta-lactams [15, 16]. Nowadays, the emergence of multidrug-resistant Gram-positive pathogens has led to resurgence in the use of vancomycin. The affected boy could not get resolve when he received vancomycin for intravenous therapy because it is hard for vancomycin to pass through the blood-brain barrier and the drug level was poor [3]. When intrathecal administration was given, it reached reasonable drug level and he got completely recover.

Generally, intrathecal or intravenous administration of vancomycin has been well tolerated in this boy, who had no obvious side effects. From the case presented here, we propose that cases of meningitis caused by EF could be treated with intrathecal and in combination with intravenous vancomycin. The combination therapy could be an effective alternative treatment for allo-CBT recipient who suffers from sepsis and meningitis caused by EF.

### Disclosure of conflict of interest

None.

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