Transfusion-related *Listeria monocytogenes* infection in a patient with acute myeloid leukaemia

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Introduction

Transfusion-transmitted infections are feared complications of blood component administration, especially in Haematology Departments, where in-patients are severely immunocompromised and at a very high risk of opportunistic infections. The incidence of transfusion-transmitted viral infections has been greatly reduced (down to less than 1 in 200,000 transfusions) across the years due to increasing awareness and control[1]. The incidence of transfusion-transmitted bacterial infections (TTBI) is currently higher, there being up to 1:60,000 infections following single unit platelet transfusions[2].

Listeria monocytogenes is a Gram-positive bacterial pathogen, which is usually foodborne[3]. Immunocompromised hosts, pregnant women, neonates and elderly people are at higher risk of developing invasive listeriosis, including central nervous system infections such as meningo-encephalitis, cerebritis or meningitis, endocarditis and sepsis caused by uncontrolled bacteraemia. Haematological patients are an important subset of immunocompromised hosts, who are frequently transfused with multiple blood components because of the nature of their haematological malignancy and the chemotherapy that has been administered.

Listeriosis caused by transfusion has not been reported in the literature yet. However, *L. monocytogenes* contamination of an apheresis platelet product was previously reported: the contamination was detected with the BacT/ALERT automated system and confirmed by pulsed field gel electrophoresis[4,5]. Here we report the first case of transfusion-transmitted *L. monocytogenes* infection in a haematological patient after the transfusion of contaminated apheresis platelets, collected from an asymptomatic donor.

Case reports

A 36-year old Caucasian female was admitted to the Haematology Department of Sant'Orsola-Malpighi Hospital (Bologna, Italy) in July 2012 with a diagnosis of acute promyelocytic leukaemia, with cutaneous and mucosal haemorrhagic syndrome.

She had no fever and her blood pressure, heart rate and oxygen saturation were normal. Induction chemotherapy with all-trans-retinoic-acid (ATRA) at a dose of 45 mg/m^2 was started. Idarubucin was not started until later.

On the 25th of July, during the transfusion of a single unit of donor-derived apheresis platelets she developed chills, with headache and vomiting; the transfusion was stopped and hydrocortisone was administered based on the diagnosis of a transfusion reaction. The adverse event was reported to the Transfusion Centre of our hospital by filling in the appropriate form. The day after, the patient had persistent fever (range 38-38.5 °C), with low systolic blood pressure and normal heart rate. Blood cultures were performed, and empirical antibiotic therapy with piperacillin-tazobactam was started, in consideration of the patient's long-standing, severe neutropenia (<500 neutrophils/μL). We recorded an increase in liver enzymes with aspartate amino-transaminase 1,214 U/L (reference <32 U/L), alanine amino-transaminase 816 U/L (reference<31 U/L), lactate dehydrogenase 1,366 U/L (reference 135-214 U/L), total bilirubin 6.98 mg/dL (reference 0.2-1.1 mg/dL), suggesting damage to the liver caused by the low cardiac output during the febrile episode.

Three days later, the patient's headache worsened, with increased blood pressure (160/110 mmHg), vomiting and photophobia, without nuchal rigidity. She underwent computed tomography of the brain which did not show density alterations. Because of the persistence of symptoms, a lumbar puncture with culture of the cerebrospinal fluid (CSF) was performed. The protein concentration was 47 mg/dL (reference <50 mg/dL), while the glucose concentration was 71 mg/dL (reference 50-80 mg/dL). Cytological examination was positive, with 400 cells/μL, including mostly neutrophilic granulocytes and occasional lymphoid cells. No blast cells were seen. Computed tomography brain scanning was repeated, with an intravenous contrast agent, and confirmed the absence of density alterations.

Blood cultures were positive for *L. monocytogenes* serotype 1/2a, which was resistant to penicillin and trimethoprim-sulphamethoxazole and sensitive to ampicillin and erythromycin. The cultured CSF was also

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positive for *L. monocytogenes* serotype 1/2a, with the same antibiotic sensitivity spectrum (Table I). Piperacillin-tazobactam therapy was switched to intravenous ampicillin 3 g every 6 hours in combination with intravenous levofloxacin 500 mg every 12 hours (favourable kinetics in the CSF). Therapy was continued for 15 days. The fever had already resolved on July 26th, whereas the neurological symptoms subsided after a few days (on August 2nd) together with normalization of the laboratory examinations.

The single-donor apheresis platelets transfused on July 25th were subsequently cultured and resulted positive for *L. monocytogenes* serotype 1/2a. Interestingly, donor blood cultures had been performed on the day of the platelet apheresis harvest and tested aerobically and anaerobically for micro-organisms; however, no micro-organisms were detected in the blood culture bottles after 7 days of incubation at 35 °C. The healthy blood donor was recalled to the Transfusion Centre and his blood was again cultured in aerobic and anaerobic blood culture bottles. This time, positive results were obtained after 31 hours. Subculture on horse blood agar revealed *L. monocytogenes* serotype1/2a.

The asymptomatic donor was investigated for possible risk factors related to the bacteraemia, such as recent ingestion of contaminated food or water or exposure to farm animals. No relation with his recent health history, environment or dietary behaviour was found. The donor was suspended from making other donations for 3 months. As repeated blood cultures were negative, the donor was subsequently readmitted and donated without problems (a new platelet apheresis was negative for *L. monocytogenes* or other bacteria).

Discussion

Our patient is the first *definite* case of transfusion-transmitted *L. monocytogenes* infection, according to the definition given by Perez *et al.* in the French BACHTEM Case-Control Study[6], with the same bacteria being isolated from both the blood product and the transfusion recipient. Furthermore, the case fits the criteria defined by the "Assessment of the frequency of Blood Component Bacterial Contamination associated with Transfusion Reaction" (BaCon) study, i.e. the occurrence of the symptoms (any one among fever ≥39 °C, rigors, tachycardia >120 bpm or a rise or drop of ≥30 mmHg in systolic blood pressure) within 4 hours after transfusion in the blood product recipient, and confirmation by culture in both the blood component and the patient[7].

Only a few similar case reports have been described in the literature, but the contaminating organisms were always identified before transfusion of the platelet product. Listeria contamination was detected by an automated BacT/ALERT system following the implementation of screening for bacterial contamination of platelet products by the American Association of Blood Banks in 2004[5]. In the report by Guevara *et al*., the donor was not interdicted from making other donations and in the subsequent month gave four other apheresis platelet donations all of which tested negative for *L. monocytogenes* contamination[4]. In our Transfusion Centre, platelets (from pools of buffy coats or from apheresis) are not routinely tested for bacterial pathogens, so we have no data regarding the frequency of *L. monocytogenes* contamination in platelet products. However, routine quality control of blood components shows that platelets may be contaminated at an expected rate (<1:1000) by exogenous environmental bacteria. However, the occurrence of a potentially life-threatening episode of TTBI has prompted us to re-evaluate the policy of screening blood products for bacterial contamination before transfusion.

The main concern related to this case is the asymptomatic *L. monocytogenes* infection in the donor, which led to a transfusion-transmitted infection in an immunocompromised patient. This is explained by transient bacteraemia (see Table I) in a donor not belonging to a high-risk group. Indeed, febrile gastroenteritis is the most common syndrome caused by listerial infection in healthy people, and it has an

Table I - *Listeria* monocytogenes isolates.

Date	Source	Cultures results	Drug sensitivity	Drug resistance
21st of July	Donor's PB (blood culture)	Negative	/	/
25th of July	Patient's PB (blood culture)	Serotype 1/2a	Ampicillin Erythromycin	Penicillin Sulpha/Trimeth
25th of July	Platelet apheresis	Serotype 1/2a	Ampicillin Erythromycin	Penicillin Sulpha/Trimeth
30th of July	Patient's CSF	Serotype 1/2a	Ampicillin Erythromycin	Penicillin Sulpha/Trimeth
1st of August	Donor PB (blood culture)	Serotype 1/2a	Ampicillin Erythromycin	Penicillin Sulpha/Trimeth

Positive cultures of the same *L. monocytogenes* serotype were obtained from the patient's and donor's blood cultures, the patient's CSF and the platelet apheresis. Sulpha/Trimeth: Sulphamethoxazole/trimethoprim: PB: peripheral blood; CSF: cerebrospinal fluid.

incubation period of about 24 hours. Invasive listeriosis with a longer incubation period can be excluded in a immunocompetent donor.

Prevention of bacterial contamination of blood products is based on donor history referral, donor examination and testing, diversion of the first flow, leucoreduction, component inspection and post-donation information[8]. Methods to improve tests for bacterial detection on platelet components before release are available, but not mandatory. Stringent screening of blood donors for TTBI is, therefore, crucial to ensure a safe supply of blood and blood products[9]. Donor questionnaires are not useful for screening out donors because *L. monocytogenes* infection in healthy individuals is normally asymptomatic. Indeed, in the BaCon study, screening 60-70% of blood banks in the United States over 3 years of active surveillance, cases of *L. monocytogenes* bacteraemia could not be identified. Risk factors for *L. monocytogenes* infection in healthy donors have not been established. Some Authors[10] have shown that iron overload is a risk factor for listeriosis. Adding questions about iron status during screening of donors could, theoretically, contribute to identifying donors at risk of bacterial infection, although the policy of people with iron overload donating blood is highly controversial[11]. It must be noted that a thorough review of the donor's behaviour did not reveal any known risk factors of exposure to *L. monocytogenes*, as also previously reported[4,5].

A bactericidal treatment such as exposure to ultraviolet light after psoralen sterilisation may be a promising method to prevent the occurrence of a TTBI[12]. In fact, photochemical treatment of platelet concentrates inactivates a broad spectrum of pathogenic bacteria, including *L. monocytogenes*[13], and 8-methoxypsoralen with long wavelength UV light (UVA) was found to be effective in reducing levels of bacteria without diminishing *in vitro* platelet function[14].

It is noteworthy that in our case the donor's blood cultures performed the same day as the platelet donation resulted negative, but when the single-donor apheresis platelet unit partially transfused to the patient was cultured, it was found to be positive for *L. monocytogenes* serotype 1/2a. This result seems to show a subsequent growth of *L. monocytogenes* in the apheresis product, occurring in the 4-day period between the day of the donation and the day of the transfusion, facilitated by the need to store apheresis platelets at room temperature.

Finally, the management of fever following transfusion is still controversial and requires cooperation between the clinician, blood bank, and microbiology services. As our case report has shown, the differentiation between an acute transfusion reaction and a TTBI in the early phase of a febrile episode during transfusion is the most difficult step. The recommendations include collecting blood from the opposite arm from that used for the transfusion and sending it for culture, performing a direct antiglobulin (Coombs') test and analysing the urine for free haemoglobin. If there is a high clinical suspicion of TTBI, empirical broad-spectrum antibiotic therapy should be started. The hospital blood bank and microbiology laboratory should also be alerted, and the blood product bag should be sent for Gram stain and culture. Moreover, if co-components from the same donation are present, they should be at least quarantined, and when leucocyte-depleted platelet concentrates obtained with the buffy coat method are transfused, all of the donors should be screened for a possible asymptomatic infection[15]. In our case, the transfusion was performed from a single donor platelets (apheresis). The plasma bag derived from the same apheresis was sent to the plasma derivation industry: a haemovigilance alert was transmitted from the Transfusion Centre to the pharmaceutical company to eliminate the plasma unit which was being held in quarantine. Improving the surveillance of the harvest, manipulation and delivery of blood products is necessary to improve transfusion safety, aided by the new pathogen inactivation techniques.

Keywords: *Listeria monocytogenes*, transfusion-transmitted infection, acute myeloid leukaemia

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