A Confirmed Ehrlichia ewingii Infection Likely Acquired Through Platelet Transfusion

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Ehrlichiosis is a tick-borne disease that ranges in severity from asymptomatic infection to fatal sepsis. Ehrlichiosis acquired from transfusion of blood products has not been documented in the literature to date. A case of Ehrlichia ewingii infection likely transmitted by transfusion of leukoreduced platelets is described, and public health implications are discussed.

Keywords. ehrlichiosis; transfusion; tick-borne; leukoreduction.

In mid-July 2011, a 9-year-old Georgia boy with a history of acute lymphoblastic leukemia and anemia secondary to chemotherapy presented to his oncologist complaining of fever, fatigue, malaise, vomiting, diarrhea, and petechial rash. He was admitted to the hospital, where cultures were performed and broad-spectrum antibiotics started to cover potential causes of sepsis. Despite antibiotic therapy, the patient’s clinical status deteriorated with worsening neutropenia, thrombocytopenia, and elevated liver enzymes. On the 11th day of symptoms, the hospital laboratory identified morulae in granulocytes on a peripheral blood smear. The patient was immediately started on doxycycline and samples were sent to Mayo Clinic for testing. Real-time polymerase chain reaction (PCR) at Mayo Clinic was positive for Ehrlichia ewingii [1], which was confirmed by further PCR testing and sequence analysis at the Centers for Disease Control and Prevention (CDC) [2]. The boy became afebrile within 48 hours of doxycycline initiation, rapidly improved, and was discharged.

Although about 32% of patients with ehrlichiosis do not recall a recent tick bite [3], this case was unusual in that the patient’s family also denied recent outdoor activity or animal contact due to the child’s illness. In addition, the patient had multiple transfusions in the month preceding symptom onset. Therefore, a possible transfusion-acquired infection was suspected, prompting the physician to contact the blood bank and the CDC. When the products the child had received were determined to come from Florida, the Florida Department of Health was notified and the Florida blood bank involved conducted trace-back investigations on the 3 donors.

The 3 transfusion products that the patient received in the month prior to onset of his illness are documented in Figure 1. All products were leukoreduced and irradiated. All 3 donors denied any symptoms of illness during the time of donation. However, 1 donor reported frequent tick attachment at his home in Florida and a wooded property in South Carolina in the month prior to donation. All 3 donors were tested by indirect immunofluorescence assay serology at the CDC, and only the donor that had reported tick exposure was positive, with an Ehrlichia species immunoglobulin G (IgG) titer of 1:512. This donor is considered the most likely source of the boy’s Ehrlichia ewingii infection.

The Ehrlichia-positive donor had regularly donated platelets or plasma collected by apheresis 1–2 times per month. He reported no febrile illnesses in the 2 months prior to and following the suspect donation. Routine complete blood counts performed by the blood bank at the time of each donation were normal. Trace-backs of other recipients receiving blood products from the positive donor between 12 May 2011 and 27 July 2011 were performed to assess if any additional recipients had symptoms relating to E. ewingii. Five recipients received leukoreduced platelets and 3 recipients received plasma from the donor (Figure 1). Three of the recipients died within 1–2 days of transfusion due to unrelated causes. The remaining 5 recipients reported no symptoms of illness associated with E. ewingii; 4 of the 5 patients agreed to be tested and were negative by Ehrlichia species serology. It should be noted that none of the 4
recipients who tested negative received products from the same donation date as the infected child.

There were no samples remaining from the incident donation, so confirmation of the donor’s diagnosis through PCR was not possible. However, a significantly elevated *Ehrlichia* species IgG titer, such as the one found in the donor (1:512), is an uncommon finding [4, 5]. This, in addition to the child’s reported lack of possible tick exposure, make transfusion the likely source of *E. ewingii* infection.

There are several unique aspects of this case that have public health importance. *Ehrlichia ewingii* belongs to a group of organisms in the family Anaplasmataceae, a group that also includes the tick-borne pathogens *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum*. These organisms reside in leukocytes, where they form clusters of organisms known as morulae that are sometimes visible by microscopy. Although it has been previously demonstrated that transfusion transmission of *Ehrlichia* species is scientifically plausible [6], this case report is the first documentation of likely occurrence in the literature. In contrast, there have been 5 published reports of *A. phagocytophilum* transmitted by transfusion of blood products [7–11].

The first 2 transfusion-transmitted *A. phagocytophilum* infections involved nonleukoreduced red blood cell transfusions [7, 11]. These initial reports, and the fact that these intracellular pathogens are typically found in leukocytes, encouraged speculation that leukoreduction may reduce the risk of transmission of pathogens in the family Anaplasmataceae. However, in 2012, 3 cases of transfusion-acquired anaplasmosis from leukoreduced blood products were reported [9, 10].

This is the first report of ehrlichiosis that was likely to have been acquired by transfusion, and the first to implicate leukoreduced platelets as the probable source of a tick-borne rickettsial pathogen. This suggests that, much like red blood cells, transfusion of platelets, even when leukoreduced, can transmit pathogens that are typically found in leukocytes. It should also be noted that the donation that was likely responsible for the transfusion-related infection was irradiated. Irradiation is not likely to kill the pathogen, or the leukocytes, but rather limits leukocyte reproduction. Physicians should be aware that irradiation or leukoreduction does not eliminate the risk of transfusion-acquired infection with this pathogen.

An additional unique aspect of this case is that the infection was confirmed to be due to a rarely reported species, *E. ewingii*, and not the more commonly reported *E. chaffeensis*. This pathogen was first documented as a cause of human disease in a 1999 publication by Buller et al [2]. Although *E. ewingii* infections may be asymptomatic in immunocompetent individuals [12], a majority of published reports have occurred in people with some form of immune compromise [2, 13]. The most common symptoms in reported *E. ewingii* infections include fever, headache, and malaise, and thrombocytopenia and leukopenia may also be present [2].

Despite the relatively low number of reported cases, *E. ewingii* is likely widely distributed throughout the central and southeastern United States [14]. Given that serology does not distinguish between *E. ewingii* and *E. chaffeensis*, it is likely that some cases of *E. ewingii* infection are missed or misclassified as *E. chaffeensis* infections [2].

It is unclear at this time why both *A. phagocytophilum* and *E. ewingii* have now been implicated in transfusion infections, whereas *E. chaffeensis* has not. Unlike *E. chaffeensis*, which targets human monocytes, *E. ewingii* and *A. phagocytophilum* are usually found in granulocytes. There is no clear evidence that this affinity for granulocytes increases transfusion risk; however, granulocytes are typically more numerous in human blood than monocytes. It may be possible that granulocytes release more pathogen into the plasma prior to leukoreduction, or remain more prevalent in postleukoreduction products than monocytes. Another possible explanation is the relative severity of symptoms caused by the various pathogens. *Ehrlichia ewingii* ehrlichiosis, like anaplasmosis, has been documented to be less likely than ehrlichiosis caused by *E. chaffeensis* to result in severe or fatal outcome [13]. It may be possible that people who are infected with *E. chaffeensis* are less likely to remain...
asymptomatic and present as donors than people infected with the more benign pathogens.

The previous reports of transfusion-transmitted anaplasmosis have described asymptomatic donors, and it appears from this case that it is also possible to remain asymptomatic during *E. ewingii* infection. This finding highlights the difficulty of preventing these pathogens from entering the blood supply. Even though our donor did recall extensive tick exposure, many people with tick-borne disease do not, and using tick exposure questions to screen potential donors is not only likely to miss cases, but also may substantially decrease the number of available donors in some regions [15]. At the present, screening all donated blood products by PCR for *Ehrlichia* species is cost prohibitive and of unknown utility [9]. Screening donors for symptoms of illness or abnormal laboratory findings such as thrombocytopenia would not have been useful in excluding this donor either. Therefore, at the present there is no screening method that can be practically implemented to prevent an asymptomatic infected donor from donating blood products. Early reporting of suspected transfusion-related infections to the blood collection agency and public health authorities is of key importance so that potentially infectious co-components may be tracked and quarantined and the infected donor and recipients can be treated.

Although in this case identification of morulae aided in making the initial diagnosis, the sensitivity of morulae detection in ehrlichiosis and anaplasmosis is low, and physicians usually need to treat the patient without confirmation of diagnosis. The recommended treatment for ehrlichiosis is doxycycline; other broad-spectrum antibiotics are not likely to be effective, and treatment delay can lead to adverse outcome or death [16]. Therefore physicians will need to consider this pathogen as a possibility early during treatment of possible transfusion-related infections and begin doxycycline treatment as soon as the disease is suspected. Given the challenges in confirmation of diagnosis, rapid empiric treatment is essential, and an astute physician is a patient’s best defense.

**Notes**

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