Coagulation and Transfusion Medicine / Transfusion-Transmitted A phagocytophilum

Two Cases of Transfusion-Transmitted Anaplasma phagocytophilum

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Abstract

Anaplasma phagocytophilum, the causative agent of human granulocytic anaplasmosis, is an obligate intracellular bacterium most commonly acquired from tick bites. High seroprevalence rates in endemic regions suggest that transfusion transmission of A phagocytophilum would be a common event; however, only 2 cases have previously been reported. The exact cause of this discrepancy is not known. Whole blood leukocyte-reduction methods used by many blood centers are thought to reduce the risk of transfusion-transmitted A phagocytophilum based on seroprevalence rates for the organism. We report 2 additional cases of transfusion-transmitted A phagocytophilum in which leukocyte reduction of all transfused units failed to prevent microbial transmission.

Upon completion of this activity you will be able to:

• describe the mode of transmission, clinical symptoms, and laboratory identification of Anaplasma phagocytophilum.
• list the areas of the United States that have the highest risk of transfusion-transmitted A phagocytophilum based on seroprevalence rates for the organism.
• discuss the benefits and limitations of screening methods for prevention of human granulocytic anaplasmosis transmission by transfusion.

Human granulocytic anaplasmosis (HGA) is caused by Anaplasma phagocytophilum, a gram-negative, obligate intracellular bacterium that has tropism for neutrophils. A phagocytophilum (formerly known as Ehrlichia phagocytophilum) is a reportable disease, which generally manifests as a nonspecific febrile illness with several possible signs and symptoms, including malaise, headaches, rigors, myalgias, and arthralgias. Rare complications include encephalitis and acute respiratory distress syndrome, with a mortality rate of 2% to 5%.1 The highest incidence rates of HGA are in the northeastern and upper midwestern states, particularly Connecticut, New York, Minnesota, and Wisconsin.1 Not uncommonly, patients seem to have unrecognized infections, as suggested by studies of seroprevalence rates compared with the reported incidence of symptomatic HGA in endemic regions of the United States and Europe.2

A phagocytophilum is most commonly transmitted to humans via the bite of a tick (Ixodes spp). The mammalian reservoirs are predominantly the white-footed mouse and other small mammals. White-tailed deer are also a common reservoir and will show persistent subclinical infections, while the mouse shows only a transient bacteremia of 1 to 4 weeks.2 Humans most often are infected when they come into contact with the tick vector in reservoir animal habitats.

Alternative modes of transmission have been reported. They have included transplacental infection of an infant3 and blood inhalation or percutaneous blood exposure following the butchering of white-tailed deer.4 Transmission by blood transfusion has been reported only twice before, once in 1999, and once in 2007.5,6 We present 2 additional cases of
transfusion-transmitted HGA, including patient and donor history, clinical course, and laboratory investigation.

**Case Reports**

**Case 1**

An 81-year-old woman with a history of rheumatoid arthritis, taking prednisone and methotrexate, was admitted in January 2010 to a community hospital following a fall and a left hip fracture. She underwent surgical repair, during which she received 2 U of leukocyte-reduced RBCs. She was released 4 days later to a rehabilitation facility with planned follow-up. Five days following discharge, she was readmitted to the hospital with fever, myalgias, and pancytopenia. She developed disseminated intravascular coagulopathy with multiorgan failure. Review of the peripheral blood smear revealed intracytoplasmic morulae consistent with HGA (Image 1). Subsequent polymerase chain reaction (PCR) testing performed on the patient’s blood sample confirmed that *A. phagocytophilum* DNA was present. She fully recovered from this infection.

Since the patient had no known risks for tick bites, transfusion-transmitted *Ehrlichia* was suspected. Two retention links from each blood donation were available for testing. A PCR test for *A. phagocytophilum* DNA was positive in 1 of the 2 products. The implicated donor had a follow-up sample obtained 2 months after the donation; serologic testing for anti-*A. phagocytophilum* showed an IgM titer of 1:40 (positive, ≥1:20) and an IgG titer of more than 1:1,040 (positive, ≥1:64), interpreted as a “current or recent infection” by the testing laboratory.

The donor was a 53-year-old man with no significant medical history. While he had no recollection of tick bites, he had been hunting in a wooded area of Wisconsin approximately 1 week before his donation. He participated in the field dressing of a deer and rabbit. The donor also owned a dog, which had also been in wooded areas recently. The donor reported no signs or symptoms of any illness from the period of interest. After counseling the donor about his test results, he was referred to his primary physician and treatment with a course of antibiotics was initiated.

**Case 2**

The patient was a 51-year-old woman with a medical history of hypertension, supraventricular tachycardia, renal insufficiency, degenerative joint disease, and multiple myeloma. In March 2007, she received an allogeneic sibling donor stem cell transplant, which initially engrafted, but later she had graft failure, in July 2007. In August 2007, the patient underwent a second nonmyeloablative stem cell transplant from the same sibling donor, which was complicated by an invasive fungal sinusitis 2 days after transplantation. She underwent emergency sinonasal debridement, and antifungal therapy was started (posaconazole and micafungin). She received 5 granulocyte transfusions during the next week, after which her WBC count spontaneously improved. Her platelet count was maintained via transfusion at this time, with a goal of more than 50 × 10⁹/μL (50 × 10⁹/L) in preparation for additional sinonasal debridement. She received 19 U of leukocyte-reduced apheresis platelets

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**Image 1** (Case 1) Neutrophils with intracytoplasmic morulae (arrows), consistent with the diagnosis of human granulocytic anaplasmosis, found during peripheral blood smear review (A, Wright stain, ×50; B, Wright stain, ×100).
(2 products were from the same donor) and 6 leukocyte-reduced RBCs during this admission; all components were collected by BloodCenter of Wisconsin (Milwaukee) with the exception of 1 unit, which was from an outside blood center. All units were irradiated (25 Gy minimum) before transfusion. The patient recovered and was discharged home on posttransplant day 17.

Owing to her chronic illness, her reported activities were limited to getting out of bed and moving to the couch. Neither she nor her caregivers participated in any outdoor activities that would have increased their potential exposures to tick bites. Seven days after discharge, she came to the outpatient clinic with complaints of feeling cold and very fatigued. She went home that night but was admitted to the hospital the following day after developing a fever of 104°F at home. On admission, she was noted to have a fever (temperature, 102.6°F), a pulse rate of 105 beats per minute, and lower extremity petechial lesions bilaterally. Her laboratory values upon admission were as follows: WBC count, 26,000/μL (26.0 × 10⁹/L); hematocrit, 29% (0.29); hemoglobin level, 10.2 g/dL (102 g/L); and platelet count, 39 × 10⁹/μL (39 × 10⁹/L). Her differential was within normal limits. She was noted to have increased liver function test results and nephrotic syndrome. Her chest radiograph was negative, and her sinus computed tomography scan showed overall improvement. Treatment with antibiotics (imipenem and vancomycin) was started. Viral studies for human herpesvirus-6, adenovirus, and parvovirus were all negative; cytomegalovirus antigen was negative. She had a urine culture that grew 200 colonies of gram-positive cocci in chains; blood cultures were negative.

Seven days after admission, an evaluation of her peripheral blood smear demonstrated intracytoplasmic morulae, resulting in a diagnosis of HGA. Doxycycline therapy was immediately started. A sample was sent for PCR, which confirmed the presence of *A phagocytophilum* DNA. Serologic tests for HGA and human monocytic ehrlichiosis, from samples collected and performed the same day, were both negative for IgG and IgM titers. The patient recovered and was discharged 13 days after admission.

There were 29 blood donors potentially implicated, 6 donors of leukocyte-reduced RBCs, and 18 apheresis platelet donors. Of the donors, 26, including all 5 granulocyte donors, returned for serologic tests within 3 to 10 months of donation and were found negative for IgG and IgM HGA antibodies. Two donors, both of RBCs, did not return after multiple requests. Both were contacted by telephone and denied symptoms of disease and known exposure to tick bites. Both of these RBC units were transfused 14 days before the patient’s return with HGA symptoms. One apheresis platelet donor could not be contacted for follow-up; this product was transfused 17 days before the patient’s symptoms.

**Discussion**

We present 2 cases of transfusion-transmitted HGA. The first case was confirmed through PCR and serologic testing. The donor did not identify one specific source of infection, such as a known tick bite, but had multiple high-risk tick exposure activities. The second case, while not having a confirmed donor source, was still likely a transfusion transmission based on the patient’s clinical history and lack of environmental sources for tick exposure.

In this second case, the patient was unlikely to have been exposed to environmental sources. The patient was out of the hospital environment for only 7 days and was mostly confined to her home owing to her clinical condition. There were no known pets in her home, and while other caregivers could potentially carry in ticks from outside, it is extremely unlikely. Even if there was a pet exposure, a study from Austria showed no increased seroprevalence for *A phagocytophilum* in cat or dog owners as compared with people with no pets, suggesting that pets are not a likely source of infection.

The evidence that supports a transfusion as the source of infection is in the timing of the transfusions. While 26 of 29 blood donors were ruled out by serologic testing, 3 were not. Two RBC units from untested donors were transfused 14 days before the patient reported symptoms, and 1 apheresis platelet unit from an untested donor was transfused 17 days prior. Of the 2 RBC donors, 1 would be the most likely source, as the time to develop symptoms of HGA is approximately 7 to 10 days.

The recent hematopoietic stem cell transplant could also be a possible source of infection. While the donor was not tested, this is not likely the source of infection. First, the transplant was 25 days before presentation with HGA, well past the expected incubation period. Second, the most recent transplant was a repeat transplant from the same sibling donor collection as the first allogeneic transplant 5 months earlier, in which no such symptoms were reported.

Transfusion transmission of *A phagocytophilum* is extremely rare, as only 2 other cases have been reported. In general, transfusion transmission of tick-borne disease is infrequent; the most common in the United States is with *Babesia*, with greater than 20 cases reported.1

Tick exposures are common in certain areas of the country. Although 1,009 cases of HGA were reported to the Centers for Disease Control and Prevention in 2008, it is likely that many infections go undiagnosed owing to the mild and nonspecific symptomatology associated with the majority of infections.5 HGA has an incubation period of approximately 7 to 10 days before the onset of symptoms. People with fevers or who are otherwise unwell would not be allowed to donate, but people who have yet to develop symptoms may not be deferred. Tick bite–specific screening questions have not proved useful, as donors usually do not remember a tick bite.
bite. Donors who do find a tick typically do so within the first 24 to 48 hours, before infective transmission is likely to have taken place; excluding these donors may limit donation by up to 9%1 in endemic regions. Deferring potential donors in disease-endemic areas during peak tick activity (April-September) would severely limit the blood supply with little potential gain. In an endemic area such as Wisconsin, where IgG seroprevalence reaches 14.5%, the chance of accepting a donor with subclinical infection is a less hazardous alternative than using serologic screening with a resultant dramatic reduction in blood supply. Furthermore, with current platforms, PCR testing of donors would be cost prohibitive and likely low yield.

Leukocyte reduction has been proposed as a method of reducing transfusion-transmitted tick-borne infections. Mettille et al9 demonstrated that leukocyte reduction successfully reduced the organism load and prevented infection using in vitro studies with Orientia tsutsugamushii–spiked blood products. Another study, by McKechnie et al,10 was able to show that viable, cell-free Ehrlichia chaffeensis in ADSOL-treated RBCs was capable of causing infection in a cell culture model; this finding suggests that leukocyte reduction alone will not prevent infection. Our products (BloodCenter of Wisconsin), including those that were transfused in both cases, were leukocyte-reduced. As this did not successfully prevent the transmission of A phagocytophilum in our cases, it suggests that leukocyte reduction, while possibly reducing the risk of transfusion transmission, does not eliminate the risk.

Clinical transfusion-transmitted HGA is fortunately a rare event. One may hypothesize, based on the discrepancy between the seroprevalence markers of infection compared with reported cases of disease in endemic areas, that transfusion-transmitted infection might be unrecognized in the majority of cases owing to low bacterial virulence. We report herein 2 cases of transfusion-transmitted HGA to heighten awareness of the issues. We do not at this time advocate screening; clinical suspicion needs to be present to help identify and treat this complication. While transfusion-transmitted A phagocytophilum infection is predominantly a risk in endemic regions, the ever-growing sharing of blood products nationally suggests that any transfusion medicine physician could encounter this complication of transfusion therapy.

References