Featured case report

**Severe life-threatening *Ehrlichia chaffeensis* infections transmitted through solid organ transplantation**


**Abstract:** Background. Donor-derived infections from organ transplantation are rare occurrences with preoperative screening practices. *Ehrlichia chaffeensis*, a tick-borne illness, transmitted through solid organ transplantation has not been reported previously to our knowledge. We present cases of 2 renal allograft recipients who developed severe *E. chaffeensis* infection after receipt of organs from a common deceased donor.

**Methods.** The 2 renal transplant patients who developed *E. chaffeensis* infection are reported in case study format with review of the literature.

**Results.** Approximately 3 weeks after renal transplantation, both patients developed an acute febrile illness and rapid clinical decline. Recipient A underwent an extensive infectious workup that revealed positive *E. chaffeensis* DNA from polymerase chain reaction on peripheral blood. Recipient B’s clinical team obtained acute and convalescent antibody titers for *E. chaffeensis*, which demonstrated acute infection. Recipients A and B were treated with doxycycline and tigecycline, respectively, with clinical cure.

**Conclusions.** These cases demonstrate that tick-borne pathogens, such as *E. chaffeensis*, can be transmitted through renal transplantation. *E. chaffeensis* can be associated with excessive morbidity and mortality, commonly owing to delay in diagnosis and poor response to non-tetracycline antibiotics. In populations with endemic tick-borne illness, donors should be questioned about tick exposure, and appropriate antibiotics can be administered if indicated.

Approximately 4 weeks after kidney transplantation, 2 recipients from a common organ donor became critically ill with an unknown febrile illness. Subsequently, human monocytic ehrlichiosis (HME) was diagnosed in both recipients. Although acquired *Ehrlichia chaffeensis* infections have been reported after solid organ transplantation (SOT), these cases are the first to our knowledge to describe the transmission of *E. chaffeensis* through SOT. We describe the presentation of a severe life-threatening syndrome and highlight the difficulty in making the diagnosis of donor-derived HME infection.

**Key words:** *Ehrlichia chaffeensis*; solid organ transplant; transplant infection; tick-borne illness; human monocytic ehrlichiosis

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**Case reports**

**Donor**

The donor was a 54-year-old Caucasian man declared brain dead in the summer of 2009 following a hemorrhagic cerebrovascular accident. His past medical history included hypertension, hyperlipidemia, cardiomyopathy, and atrial fibrillation with chronic anticoagulation with warfarin. He also had hepatitis C viremia, with attributed chronic thrombocytopenia.
He was in his usual state of health until the month before admission, when he experienced fatigue and joint pains, prompting laboratory testing for Lyme disease, which was negative. Arthralgia and fatigue continued, and he began to experience diaphoresis, chills, dyspnea, and chest pain. He never experienced fever or rash. The day before admission, he complained of leg pain and his lower extremities were covered with “deep red specks.” He was admitted with pain and swelling of his right lower extremity, and diagnosed by duplex Doppler ultrasound with a deep vein thrombosis. His international normalized ratio (INR) was elevated and he had hematuria and hematochezia. On the night of admission, he was found unresponsive and apneic. Computed tomography scan of the brain revealed a large cerebellar hemorrhage, and he was declared brain dead on the day after admission.

Donor workup included negative urine, blood, and sputum cultures. He was negative for human immunodeficiency virus (HIV) 1/2, human T-lymphocyte virus 1/2, hepatitis B surface antibody and antigen, rapid plasmin reagin, toxoplasmosis antibody, and Chagas disease antibody. His positive serologies included cytomegalovirus (CMV), hepatitis C virus, and Epstein–Barr virus (EBV). Liver biopsy revealed stage 4 cirrhosis.

He lived on a wooded lot located in the southern portion of Maryland, on the western shore of the Chesapeake Bay. According to his family, he took 30–60 min walks in the woods regularly, the last being in the month before his symptom onset. He frequently found attached ticks after returning from these walks. He had no significant interactions with wildlife, but had a cat and dog that spent time outdoors. He had no recent travel outside of Maryland.

**Recipient A**

A 57-year-old African-American woman with end-stage renal disease secondary to hypertension received the deceased-donor renal transplant from the donor 2 days after his declaration of brain death. Her past medical history included hepatitis C, dyslipidemia, pancreatitis, and gastroesophageal reflux disease. Her immunosuppression regimen consisted of tacrolimus, mycophenolate mofetil, and prednisone. She received induction therapy with anti-thymocyte globulin. Her anti-infective prophylaxis regimen consisted of valganciclovir, trimethoprim-sulfamethoxazole. She was also taking pantoprazole and clonidine. She resided in an urban area and had no outdoor activities.

She presented 22 days after renal transplantation with complaints of fever for 2 days. She was noted to have dysuria, and a presumptive diagnosis of a urinary tract infection was made, and she was prescribed levofloxacin. Her fever persisted and she developed pain at her renal transplant site, new onset low back pain, anorexia, and one episode of non-bloody, nonbilious vomiting. She had no risk factors or exposure history to tick bites and no rashes.

On admission, her blood pressure was 98/67 mmHg, pulse 102 beats/min, and temperature 39°C (102.2°F). Her renal allograft site was tender, firm, but not enlarged. A renal ultrasound was suggestive of acute tubular necrosis. Urine culture grew 20,000 colonies of *Staphylococcus aureus*. Vancomycin and ceftriaxone were started. She remained febrile and her renal function worsened. Kidney biopsy showed isometric vacuolization of tubules possibly consistent with tacrolimus toxicity, but not rejection. By hospital day 4, she had progressive pancytopenia, worsening mental status, and pulmonary effusions and infiltrates. A computed tomography scan of the brain, lumbar puncture, and bronchoscopy studies were unremarkable. She required intubation and hemodialysis. Thrombotic microangiopathy was considered, but analysis of her peripheral smear and renal biopsy did not support the diagnosis.

Antimicrobial coverage was broadened with cefepime, caspofungin, and ganciclovir. Evaluation for toxoplasmosis, CMV, varicella zoster, EBV, herpes simplex virus 8, parvovirus 19, West Nile virus, herpes simplex virus, *Legionella*, syphilis, peripheral smear for malaria, HIV, Cryptococcus, and *Aspergillus* were all negative. Hepatitis C quantitative viral load was 191,000 IU/mL; hepatitis B surface antigen was negative. She was started empirically on doxycycline on hospital day 5. The patient’s condition began to improve 5 days after starting doxycycline. Gradually, her renal function improved and hemodialysis was discontinued. Repeat kidney biopsy was not consistent with tacrolimus toxicity or acute rejection. See Table 1 for Recipient A laboratory results.

**Recipient B**

A 56-year-old African-American man received the second kidney from the same donor as Recipient A for hypertensive nephropathy. His past medical history included hepatitis C with early fibrosis, remote history of intravenous drug use, hyperlipidemia, sleep apnea, and secondary hyperparathyroidism. Immune suppression post transplantation was achieved with mycophenolate
mofetil, tacrolimus, and prednisone. The patient received basiliximab induction. His anti-infective prophylaxis regimen was valganciclovir, clotrimazole, and trimethoprim-sulfamethoxazole. Other medications included metoprolol, simvastatin, furosemide, paroxetine, cinacalcet, and calcium supplements.

He was admitted to the hospital 25 days after transplantation with a temperature of 39.5°C (103°F) and a discharge from his surgical wound. He was treated with vancomycin and pipercillin/tazobactam empirically for a likely surgical site wound infection. Like Recipient A, he resided in an urban area and denied spending time outdoors. He had no risk factors or exposure history to tick bites and no rashes.

On hospital day 3 (postoperative day 27), the patient was noted to have an acute onset of confusion rapidly progressing to lethargy, with heart rate 96 beats/min, blood pressure 108/75 mmHg, temperature of 38°C (100.5°F), and new thrombocytopenia, worsening anemia, transaminase elevation, and acute anuric kidney failure. Guided drainage of the residual perinephric collections was performed; hemodialysis was initiated; and a renal ultrasound was unremarkable. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) was also considered, but schistocytes were not visualized on peripheral smear and his clinical picture was most consistent with severe disseminated intravascular coagulation.

An expanding neck hematoma resulted from central line placement, necessitating endotracheal intubation for respiratory protection. The patient had spontaneous and copious hemorrhaging from access sites, lungs, rectum, and surgical wounds. He was treated with a continuous infusion of fresh frozen plasma and ultimately required 72 U of blood products including 36 U of packed red blood cells, 28 U of fresh frozen plasma, and 8 U of platelets. Empiric antibiotic coverage was changed to cefepime, metronidazole, and micafungin. Blood, sputum, and abdominal drainage fluid cultures were all negative. A urine culture grew vancomycin-resistant Enterococcus. Serum polymerase chain reaction (PCR) for CMV, EBV, and HIV, and nasal wash for influenza and respiratory syncytial virus PCR were negative. Comparative laboratory data are noted in Table 2, with other notable labs including a peak total bilirubin of 4.4 mg/dL, INR of 1.4, prothrombin time of 17.5 s, partial thromboplastin time of 110 s, and lactate dehydrogenase of 701 U/L.

The possibility of a transplantation-derived infection was considered and the transplant network facilitated cross-communication with Recipient A’s care team, who indicated their suspected diagnosis of HME. Given the clinical picture, empiric treatment was initiated on hospital day 12 (postoperative day 38). Because of a concurrent vancomycin-resistant Enterococcus urinary tract infection, tigecycline was selected rather than doxycycline. The patient had a rapid improvement with resolution of his coagulopathy and returned to his baseline mental status 48 h after initiation of tigecycline. Renal biopsy on day 44 was consistent with antibody-mediated rejection with C4d positivity, and the patient was started on a high-dose steroid pulse, plasmapheresis, and 2 doses of human immunoglobulin. He was hospitalized for 4 weeks. On discharge, his

### Table 1

<table>
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<th>Test</th>
<th>Recipient A laboratory results</th>
<th>Post-transplant day</th>
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<tr>
<td></td>
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<td>23</td>
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<tr>
<td>WBC (k/mcL)</td>
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<td>PLT (k/mcL)</td>
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<tr>
<td>ALT (units/L)</td>
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</tr>
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</table>

1Doxycycline was initiated on day 27 post transplant.

WBC, white blood cell count; PLT, platelets; Hgb, hemoglobin; Cr, creatinine, AST, aspartate aminotransferase; ALT, alanine aminotransferase.

### Table 2

<table>
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<td>WBC (k/mcL)</td>
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<td>AST (units/L)</td>
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<td>92</td>
</tr>
<tr>
<td>ALT (units/L)</td>
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<td>54</td>
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</tbody>
</table>

1Intubated, hemorrhaging, multiple blood products transfused.
2Serotonin releasing assay ordered: borderline. Not consistent with heparin-induced thrombocytopenia.
3Baseline creatinine for Recipient B.

WBC, white blood cell count; PLT, platelets; Hgb, hemoglobin; Cr, creatinine, AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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kidney function had improved and dialysis was discontinued.

**Diagnosis**

In Recipient A, initial *Ehrlichia* serology was negative, immunoglobulin (Ig)M and IgG titers of <1:20 and 1:128, respectively, but *E. chaffeensis* immunoglobulin (Ig)M and IgG titers of <122 were negative when tested on post-transplant day 40. Repeat serologic testing was strongly positive for *E. chaffeensis*. At 12 months, serum IgG was ≥1024 titer (normal <64), and IgM ≥320 titer (normal <20). Surprisingly, antibodies for *Anaplasma phagocytophilum* IgG were also positive (IgG = 512 H titer [normal <64]), and IgM negative <20 titer (normal <620). At 18 months, repeat *E. chaffeensis* IgG = 256, and IgM <20. Serum real-time DNA PCR testing for *E. chaffeensis*, *Ehrlichia ewingii*, and *A. phagocytophilum* was negative at 18 months post transplant.

After consultation with the Centers for Disease Control and Prevention (CDC), transplant kidney biopsy specimens were sent from both patients. Patient A had 2 biopsy specimens; the first biopsy specimen tested positive on PCR for *E. chaffeensis*. The second biopsy, after doxycycline therapy, was PCR negative. The kidney biopsy specimen from Recipient B, taken after initiation of tigecycline, was PCR negative for *E. chaffeensis*. Unfortunately, no donor serum or tissue was available for serologic or PCR analysis. No other tissues or organs were donated to other patients.

Despite the inability to confirm infection in the donor, the cases establish a strong suspected transmission event and clear laboratory evidence of infection in both organ recipients. Using the Organ Procurement and Transplantation Network/United Network for Organ Sharing Disease Transmission Committee criteria, these cases would be classified as "probable" donor-derived transmission events AA1 (1).

**Discussion**

Various donor-derived infections in transplant recipients have been reported including HIV, hepatitis C virus, lymphocytic choriomeningitis virus and a related arenavirus, tuberculosis, West Nile virus, rabies, Chagas disease, *Strongyloides*, and amoeba (1–11). Case reports have described ehrlichiosis in immunosuppressed patients including transplant recipients of liver, lung, pancreas, heart, and kidney (12–18). In 1995, HME was first reported in a patient who had undergone a previous stem cell transplant (19). Although human granulocytic anaplasmosis (HGA) was first reported in a solid organ transplant patient in 1997 (20), our 2 patients are the first documented cases, to our knowledge, of transmission of *E. chaffeensis* from a deceased organ donor to organ recipients.

Laboratory findings often include leukopenia, thrombocytopenia, and elevated liver enzymes. Elevated serum creatinine and anemia can also be seen in HME (21–26). Although one review identified 15 transplant patients having similar and favorable outcomes compared with immunocompetent patients (14), in our experience, the clinical presentation of HME and HGA acquired after SOT can be severe.

The first human cases were identified in the mid 1980s (27), and subsequently the 2 main clinical diseases are known as HME caused by *E. chaffeensis* (28), and HGA caused by *A. phagocytophilum* (29, 30). Many patients give a history of tick exposure prior to presentation, with peak incidence of disease occurring in the summer months of May through August in North America (31).

The usual incubation period for *E. chaffeensis* is recognized by the CDC to be 7–14 days (32). These 2 cases illustrate a delay in onset of illness of approximately 20 days. HME can present either as an acute or subclinical illness and is typically self-limiting in a normal host. The usual presenting symptoms include fever, malaise, myalgia, arthralgia, and severe headache (33). Severe cases of HME have described renal failure and respiratory failure. A life-threatening illness with fever and acute respiratory distress syndrome, with similarities to toxic shock syndrome, has also been described (21, 22). Pulmonary hemorrhages have been observed in human patients and in as many as 60–70% of fatal infections with *Ehrlichia canis* in dogs (23).

Transplantation-related immunosuppression and an initial delay in diagnosis likely contributed to the unusually severe, life-threatening presentation, and the complicated hospital course that both patients experienced (32). These cases clearly highlight the difficulty in diagnosis of HME, especially when donor derived, and compounded by the fact that neither patient had any history suggestive of tick exposure. In addition, both patients were initially admitted with the presumptive diagnosis of postoperative bacterial infections, frequently seen after kidney transplantation. The presenting signs of renal failure, leukopenia, and
anemia are also commonly seen in renal transplant recipients. Both cases presented with fever, renal failure, thrombocytopenia, and mental status changes, raising initial clinical suspicion for post-transplantation TTP-HUS, although renal biopsy and smear analysis ruled this out. Common to both patients was the rapid development of a febrile sepsis syndrome in the absence of bacteremia and without identification of morulae in peripheral smears. The persistent and extensive infectious disease evaluation led to a diagnosis in Recipient A, and the unusually severe disseminated intravascular coagulation with life-threatening extensive hemorrhagic complications prompted the consideration of a transplant-derived infection in Recipient B.

The criteria for diagnosis of *E. chaffeensis* include serologic evidence of elevated IgG antibody reactive with *E. chaffeensis*, antigen by indirect fluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA), dot-ELISA, with IFA IgG cutoff of ≥1:64. A 4-fold change in convalescent IgG-specific antibody titers by IFA between paired serum samples tested 3 weeks after initial symptom presentation has a sensitivity of >90% (1). DNA in a clinical specimen by PCR assay also meets criteria for confirmed diagnosis. The initial absence or low titers of IgG and IgM seen in both cases highlight the difficulty of an early diagnosis of *E. chaffeensis*. In the first week after clinical symptoms of HME occur, PCR and IgM serology have a sensitivity of 60–85% and 22–55%, respectively (34). Although morulae seen on a Wright stained peripheral smear are the most rapid diagnostic test, the sensitivity is reported at 2–38% and thus not used as a diagnostic criterion (35). Furthermore, doxycycline therapy decreases the sensitivity of peripheral smear and PCR (36). This dichotomy that human ehrlichiosis infection can be rapidly progressive, fatal, and difficult to diagnose, but easily treatable, argues that doxycycline therapy should be immediately started while attempts at laboratory confirmation are initiated. Compounding the difficulty in diagnosis, it is also known that ticks may simultaneously transmit several pathogens at once, including HGA, babesia, and tularemia, and these should be considered as well. The 85% specificity seen for HME serology is a result of cross-reactivity to HGA, and likely the cause of the subsequent detectable HGA serology in Recipient B (37).

Given the increasing numbers of reported HME infections and the difficulty in diagnosis, under-diagnosis is possibly occurring in the post-transplantation period for this life-threatening, but otherwise easily treatable, illness. The similarities in the 2 cases, including the initial considerations of TTP-HUS and the severe disseminated intravascular coagulation presenting in the fourth week after transplantation, should prompt the inclusion of HME infection in the differential diagnosis in post-transplantation culture-negative sepsis syndrome. In addition, the prompt resolution of symptoms after the initiation of drugs from the tetracycline class in these 2 cases provides a strong argument for empirical use of tetracycline-class antimicrobials for similar syndromes in transplant recipients.

The recognition that HME can be transmitted through SOT, taken together with challenges in diagnostic testing, and the increasing incidence of HME infection requires a high degree of clinical suspicion about donors from high-endemic regions. Patients with undiagnosed thrombocytopenia or leukopenia, particularly with a history of an undifferentiated febrile syndrome at the time of death, should prompt the diagnostic consideration of HME infection. Unfortunately, it was only in retrospect that the presenting history gathered from the donor’s record was recognized as an obvious risk factor for tick-borne infections and an illness consistent with HME.

Finally, this case report brings to light the substantial morbidity and mortality among SOT recipients when donor-derived transmission of infection occurs. Communication between transplant centers likely saved the life of Recipient B. When donor-derived infections are suspected, communication is of vital importance, and should be a routine and expected practice.

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References


