Leuconostoc pseudomesenteroides blood stream infection following liver transplantation

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Summary

Background: Leuconostoc spp. are vancomycin resistant Gram positive lactobacilli. Little is known about their significance in transplant recipients.

Case Report: A 64-year-old female liver transplant recipient developed Leuconostoc sepsis originating from a bile leak after extended exposure to vancomycin. The infection was readily controlled clindamycin, however, the patient died later on unrelated to the infection. Five articles on Leuconostoc infections in transplant patients were found in PubMed including two liver recipients with intraabdominal infection due to biliary complications and four stem cell recipients with sepsis.

Conclusions: Leuconostoc spp. should be considered pathogens in transplant recipients who are exposed to vancomycin.

Key words: transplantation • sepsis • Leuconostoc spp. • immunosuppression


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BACKGROUND

*Leuconostoc spp.* used to be listed members of the *Streptococcaceae* family and now are recognized as *Leuconostocaceae* placed within the order of *Lactobacillales*. The organism has been first described by the French botanist van Tieghem in the nineteenth century. *Leuconostoc mesenteroides* is the most commonly described subtype with other species being *L. lactis, L. amelobiosum, L. holzapfelii, L. carnosum* and *gelidum* amongst many others. Only few have been implicated in human disease and *Leuconostoc* is best known as part of the bacterial flora that ferments cabbage into sauerkraut by converting sugars into lactic acid [1].

The Gram-positive vancomycin-resistant pathogen is emerging as a rare cause of bacteraemia in severely ill and immunocompromised hosts [2]. Most reported cases were blood stream infections, however, also meningitis, pneumonia, endocarditis, pleural empyema, osteomyelitis and urinary tract infection were described [3–10]. *Leuconostoc spp.* may be misidentified as streptococci but resistance to vancomycin is characteristic and new technologies have facilitated identification [11–14]. The new lipoglycopeptide daptomycin is active against this rare pathogen [13,15]. Clindamycin has been widely used for treatment; linezolid has emerged as a new option. Only little data are available on the significance of this pathogen in the setting of solid organ or stem cell transplantation. We report on a liver recipient who developed intraabdominal infection and sepsis with *Leuconostoc pseudomesenteroides*. In addition we report our experience with *Leuconostoc* infections during a twelve months period and PubMed was searched for clinical cases of *Leuconostoc* infection in transplant recipients.

A case report of the index infection is given in detail. The institutional microbiological database was searched for cases of *Leuconostoc* infection in 2007. PubMed was searched for *Leuconostoc* infections in transplant recipients.

CASE REPORT

Our patient was a 64-year-old Caucasian female liver recipient, who been diagnosed with primary biliary cirrhosis in 1999 by liver biopsy, when she had become symptomatic with jaundice and urticaria and blood chemistry demonstrated elevated liver function enzymes and bilirubin. She also tested positive for anti-mitochondrial antibodies. She received treatment with ursodesoxycholic acid and hydroxyzine. Comorbidities included emphysema/COPD and Sjogren’s syndrome which was treated with hydroxychloroquine. Living donor liver transplant was performed in April 2007 using the right lobe of her son (graft weight was 930 gram). A temporary portocaval shunt was used and the splenic artery was ligated to improve arterial blood flow to the graft. Biliary reconstruction was performed with a Roux-en-Y hepatojejunostomy, with two separate anastomoses due to the presence of two segmental ducts. Perioperative antibiotic prophylaxis consisted of piperacillin/tazobactam for 24 hours and immunosuppression included tacrolimus, mycophenolate-mofetil and a steroid taper. The post LT course was complicated by an anastomotic bile leak. Exploratory laparotomy on day 3 post LT revealed biliary peritonitis. The distal portion of segment 6 and 7 bile duct was necrotic and therefore, the anastomosis was revised and secured with an omental flap. Antibiotic therapy included ciprofloxacin, vancomycin and fluconazole. The patient tolerated this procedure well and slowly recovered. However, on day seven post LT she developed fever and leucocytosis and CT scan revealed a large splenic infarct and a new low-density fluid adjacent to the tip of the right surgical drain suspicious for a recurrent biloma. A percutaneous transhepatic cholangiography (PTC) with biliary catheter placement was performed and antibiotics were started. On day 14 post LT a liver biopsy was performed, which demonstrated acute cellular rejection, which was successfully treated with bolused steroids. She was discharged from hospital on day 20 post LT in satisfactory condition without sign of infection and stable graft function. TMPs was given for PCP prophylaxis. Two weeks later she returned with failure to thrive and CT scan demonstrated a partial small-bowel obstruction, a small biloma and had a superficial wound infection. She also had developed CMV infection (positive PCR) and was started on ganciclovir. Broad spectrum antibiotics included Piperacillin/tazobactam, vancomycin and fluconazole. PTC revealed good placement of the biliary catheter with minor leakage from the anastomosis. Blood cultures tested positive for *Leuconostoc pseudomesenteroides* with catheter cultures becoming positive two days later. Clindamycin (600mg thrice daily) was started and blood cultures became negative one week later. She continued to have biliary drainage through her wound. Urinary tract infection was treated with ciprofloxacin and lateron switched to linezolid after isolation of VRE. She also developed *Candida esophagitis*, which was treated with fluconazole. She was discharged in fair condition.
but required frequent emergency room visits for chronic pain, dehydration, malnutrition and failure to thrive. She died several weeks later without signs or infection from multi organ failure without evidence for recurrent leuconostoc infection.

**Institutional experience with Leuconostoc infections**

During 2007 a total of five cases (8 isolates) of *Leuconostoc* infection were observed at our hospital including the reported case. There were two blood stream infection, one urinary tract infection and two intraabdominal infections. Species included *L. pseudomesenteroides* (three patients), *L. mesenteroides* (one patient) and in one patient species identification was not performed.

**PubMed literature search**

A total of six transplant patients with Leuconostoc infection have been reported in the literature [16–19]. Four had a stem cell transplant and two like our patient had a liver transplantation. Table 1 summarizes the seven cases. All stem cell recipients had blood stream infection and all liver recipients (including our patient) had intraabdominal infection originating from biliary complications.

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**Table 1. Reported cases of Leuconostoc infections in transplant recipients.**

<table>
<thead>
<tr>
<th>Organ</th>
<th>First author</th>
<th>Title</th>
<th>Journal</th>
<th>Year</th>
<th>Site of infection</th>
<th>Origin</th>
<th>n patients</th>
<th>Intensified IS</th>
<th>Comments</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Tholpady S</td>
<td>Leuconostoc pseudomesenteroides blood stream infection in a liver transplant recipient: case report and review of the literature</td>
<td>Index Case</td>
<td>2007</td>
<td>Biliary tree, blood stream</td>
<td>Charlottesville, VA, USA</td>
<td>1</td>
<td>Rejection</td>
<td>Infection developed after treatment of intraabdominal infection (bile leak) with vancomycin</td>
<td>Clindamycin</td>
<td>Cure</td>
</tr>
<tr>
<td>Liver</td>
<td>Espinoza R</td>
<td>Leuconostoc bacteremia after liver transplantation: another cause of vancomycin resistant gram-positive infection</td>
<td>Clin Transplant</td>
<td>1997</td>
<td>Blood stream originating from peritonitis HAT, bile leak</td>
<td>Pittsburgh, PA, USA</td>
<td>1</td>
<td>No</td>
<td>Re transplant for primary non function; infection developed after treatment of intraabdominal infection (bile leak) with vancomycin</td>
<td>Clindamycin, Gentamicin</td>
<td>Fatal</td>
</tr>
<tr>
<td>Liver</td>
<td>Montejo M</td>
<td>Abdominal abscess due to leuconostoc species in a liver transplant recipient</td>
<td>J Infect</td>
<td>2000</td>
<td>Liver abscess due to cholangitis (bile duct stricture)</td>
<td>Bilbao, Spain</td>
<td>1</td>
<td>No</td>
<td>complicated post liver transplant course: renal failure, CMV disease</td>
<td>Piperacillin/Tazobactam</td>
<td>Cure</td>
</tr>
<tr>
<td>Stem cell</td>
<td>Giraud P</td>
<td>Leuconostoc, a potential pathogen in bone marrow transplantation</td>
<td>Lancet</td>
<td>1993</td>
<td>Blood stream</td>
<td>Toulouse, France</td>
<td>1</td>
<td>No</td>
<td>Infection developed after treatment of MRSA pneumonia with vancomycin</td>
<td>No therapy</td>
<td>Fatal</td>
</tr>
<tr>
<td>Stem cell</td>
<td>Golan Y</td>
<td>Daptomycin for line-related Leuconostoc bacteraemia</td>
<td>J Antimicrob Chemother</td>
<td>2001</td>
<td>Blood stream, line sepsis</td>
<td>Boston, MA, USA</td>
<td>2</td>
<td>GvHD, leukemia, relapse</td>
<td>Both infections developed after exposure to vancomycin</td>
<td>Daptomycin</td>
<td>Cure</td>
</tr>
<tr>
<td>Stem cell</td>
<td>Yamazaki R</td>
<td>Leuconostoc septicemia in a neutropenic patient with acute myelogenous leukemia relapsed after allogeneic peripheral blood stem cell transplantation</td>
<td>Transpl Infect Dis</td>
<td>2009</td>
<td>Blood stream, line sepsis</td>
<td>Tokyo, Japan</td>
<td>1</td>
<td>GvHD</td>
<td>Infection developed after treatment of febrile neutropenia with teicoplanin</td>
<td>Ampicillin/Gentamycin</td>
<td>Cure</td>
</tr>
</tbody>
</table>
One liver recipient had rejection, two stem cell recipients had Graft versus host disease and another recurrent leukemia. All except one patient had been exposed to vancomycin or teicoplanin prior to Leuconostoc infection. Treatment consisted of clindamycin in two patients (including our patient), a combination of ampicillin with gentamycin in another individual; piperacillin/tazobactam was used once and two patients were treated with daptomycin (one patient died before initiation of therapy). Fatality rate of reported Leuconostoc infections in transplant recipients was 29%.

**DISCUSSION**

The spectrum of pathogens involved in transplant recipients is constantly expanding. MRSA and Enterococcus faecium are important and common pathogens in this patient population and these two pathogens usually are covered in an empiric treatment course in transplant candidates and recipients. Therefore, transplant recipients are frequently exposed to glycopeptides. This happens not only during the pretransplant period for infections associated with the underlying terminal organ failure but also post transplant in the case of surgical complications or other infections. This leads to an excessive risk to select pathogens that are resistant to vancomycin in particular in the case of chronic infections, graft failure, comorbidities and in those patients who are exposed to intensified immunosuppression. Six of the seven patients with post transplant Leuconostoc infection had been exposed to glycopeptides. Of note, in a substantial number of so called “non well doers” multiple such risk factors are present. All three reported liver transplant recipients had biliary complications. VRE is by far the most common such pathogen and a significant problem in transplant medicine, however, also other rarer pathogens may emerge [20]. *Leuconostoc spp.* are considered friends of humans. They are commensals of the mucosa but there seems to be racial differences in the colonization pattern [21,22]. Medline brings up more than 1650 publications on this pathogen, however, only a fraction deals with human diseases. The first article on this organism dates back to 1943, when Gaines et al. reported on the growth requirements of *Leuconostoc mesenteroides* and preliminary studies on its use as an assay agent for several members of the vitamin B complex [23]. *Leuconostoc* has been used as a model to study metabolic cellular processes, it has been used for industrial production of dextran from dextransucrose but most importantly the organism has been extensively studied for the purpose of food preservation [24–28]. Depending on the cultural background, *Leuconostoc* and other lactobacilli are used to prevent spoilage of foods and aromatizing them [29]. This includes cabbage fermentation to sauerkraut, fermentation of wines, coffee and production of “stinky tofu” amongst many other applications [1,30–33]. *Leuconostoc* is capable to prevent colonization of food with *Staphylococcus aureus, Listeria monocytogenes* and enteric pathogens such as *Salmonella* [34–36]. This is also well acknowledged by the fact that *Leuconostoc spp.* are frequently part of pro and prebiotic foods and even medical preparations such as tube feeds. Only recently, probiotics have been recognized as a possible source of bacteremia in severely immunosuppressed individuals [37,38]. In most cases, neutropenia in the setting of hematological malignancies was present, however, *Leuconostoc* has also been isolated in a patient with short bowel syndrome [39]. It may also isolated from gastric aspiration in patients with gastric cancer [40]. As far as our patient, the surgical complication of a bile leak caused intraabdominal infection and subsequently a biliary stent was placed. This served as a chronic source of infection. The patient was exposed for a prolonged time to vancomycin, which ultimately lead to selection of a resistant organism. In the reported case it was *Leuconostoc*, which is unique, as at our institution VRE has become the predominant organism in these settings. The pretransplant poor medical condition and cachexia as well as immunosuppression and application of parenteral nutrition and enteral tube feeding may all have been contributing factors [41].

**CONCLUSIONS**

In light of the recent increase in the use of vancomycin, one must be aware that VRE are not the only resistant Gram positive bacteria that need to be considered. *Leuconostoc spp.* may be under-appreciated human pathogens.

**Statements**

No conflicts of interest and no financial disclosures are to be reported. The article was written in compliance with the University of Virginia Ethical committees recommendations.

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