ELSEVIER

Hemorrhagic Pneumonia in a Kidney Transplant Recipient Caused by *Stenotrophomonas Maltophilia* Infection: A Case Report

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ABSTRACT

Pneumonia is a common nosocomial complication in transplant patients. *Stenotrophomonas maltophilia* is recognized as a common cause and is typically seen in immunocompromised and critically ill patients. *S. maltophilia*, a nonfermenting gram-negative rod, ranks as the third most common nosocomial pathogen, following *Pseudomonas aeruginosa* and *Acinetobacter*. The bacteria are frequently found in environmental sources and are prevalent in healthcare facilities, including in tap water faucets, shower outlets, air-cooling systems, intravenous fluids, catheters, dialysis machines, and oxygen humidifiers. This bacterium possesses the ability to rapidly form biofilms, enabling it to colonize new surfaces in less than 24 hours. While *S. maltophilia* generally exhibits low virulence, there remains uncertainty among many clinicians regarding whether it is merely a colonizer or the primary cause of infection. Although *S. maltophilia* infections are rare in immunocompetent individuals, the species is increasingly recognized as an opportunistic pathogen in vulnerable populations such as those with cystic fibrosis, cancer, and other conditions leading to immunosuppression. *S. maltophilia* now recognized as a causative agent in various clinical syndromes, primarily affecting the lungs and bloodstream. We present a case of *S. maltophilia*-associated lung infection in a kidney transplant recipient, emphasizing the significance of underlying diseases and associated signs and symptoms.

CASE PRESENTATION

OUR patient was a 73-year-old man, whose medical history included type 2 diabetes, hyperuricemia, diabetic nephropathy, a deceased donor kidney transplant in 2016, atrial fibrillation, and insertion of drug-eluting stents in the left anterior descending artery in 2018 and circumflex coronary artery in 2019. Additionally, he had stents implanted in the right internal carotid artery in 2022. He had multiple hospitalizations for cardiovascular decompensation. His final urgent hospital admission was prompted by symptoms of dyspnea, chest pain, and respiratory failure- that were attributed to a non-ST-elevation myocardial infarction caused by restenosis in the circumflex artery which led to cardiac decompensation, primarily. The patient needed mechanical ventilation, drug-eluting stent (resolute integrity zotarolimus-eluting coronary stent) placement, and continuous venovenous hemodiafiltration. He subsequently developed pneumonia.

Upon initial treatment with cephalosporin, the patient developed diarrhea. A confirmed Clostridium difficile infection led to the initiation of oral vancomycin therapy, successfully resolving the clostridial infection. Subsequent urine culture revealed *Pseudomonas aeruginosa*, and *Enterococcus faecalis* was identified in the bloodstream. Due to the patient's immunosuppressed state resulting from everolimus and methylprednisolone therapy, the antibiotic regimen was adjusted in collaboration with infectious disease specialists to, incorporate carbapenem, tigecycline, and micafungin.

When the pneumonia became controlled, mechanical ventilation was discontinued. However, the patient experienced a recurrence of diarrhea. The abdominal ultrasound revealed thickening of the colon wall and signs of intestinal inflammation. Despite negative fecal cultures, tigecycline therapy was continued along with carbapenem therapy, considering the previous bloodstream infection. The drug levels of everolimus

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exceeded the therapeutic range (12- 34 ug/L, therapeutic range: 3-8 ug/L) during the treatment, so its dose was reduced. The drug level returned to within the therapeutic range by the end of the third week of treatment.

In the fourth week of treatment, the patient suddenly developed rapid-onset weakness in his leg muscles, which peaked within 2 days. Imaging studies, including cranial computed tomography (CT) scan and spine magnetic resonance imaging, did not reveal any abnormalities.

Laboratory tests indicated a platelet count of 59 × 10^9/L, a white blood cell count (WBC) of 14.4 giga/L, a potassium concentration of 5.8 mmol/L, a procalcitonin (PCT) concentration of 1.5 μg/L, and a C-reactive protein (CRP) concentration of 78.52 mg/L.

Additionally, the results showed positive viral capsid antigen and nuclear antigen of the Epstein−Barr virus (EBV-VCA-IgG positive, EBV-EBNA IgG positive, and EBV qPCR positive at 9755 IU/mL), as well as positive herpes simplex virus (HSV) IgM (Herpes simplex 1/2 PCR positive). The presence of ascending paresis with positive EBV and HSV tests raised the suspicion of Guillain−Barré syndrome, confirmed by positive electroneurogram (ENG) results. Consequently, treatment involving antiviral drugs and intravenous immunoglobulin (IVIG) therapy was initiated. Subsequently, the patient complained of dyspnea again, without cardiac decompensation. A chest CT scan revealed bilateral pleural effusion, ground-glass opacity in the right lower lobe, diffuse patchy infiltrates measuring up to 10 mm in maximum size, and an approximately 8 mm pericardial effusion (Fig. 1).

Despite thrombocytopenia, the cardiologist recommended continuing ticagrelor therapy due to the patient's cardiac stent. Within 2 days, the patient's condition rapidly deteriorated, necessitating transfer to the intensive care unit (ICU), where mechanical ventilation was initiated because of worsening respiratory failure. Flexible bronchoscopy with bronchoalveolar lavage revealed both fresh and old blood in the right lower lung lobe. In response to septic shock and acute kidney failure, a combined therapeutic approach was initiated, involving continuous veno-venous hemodiafiltration and extracorporeal cytokine adsorber. Bacterial culture samples (respiratory, blood, skin, urine) were repeated then antibiotic therapy was changed to ceftazidime−avibactam, aztreonam, and trimethoprim/sulfamethoxazole (TMP-SMX) continuing the tigecycline therapy.

Upon admission to the ICU, the patient's laboratory values were as follows: interleukin-6 (IL-6) 506 ng/L, creatine kinase (CK) 7208 U/L, lactate dehydrogenase (LDH) 763 U/L, glutamic oxaloacetic transaminase (GOT) 210 U/L, cardiac troponin 72.25 ng/L, activated partial thromboplastin time (APTT) 55 sec, and D-dimer 0.96 FEU/L, platelet count 43 G/L, WBC 3.5 G/L, red blood cell count (RBC) 2.8 T/L, CRP 116 mg/L, and PCT 1.5 μg/L.

All bacterial culture results (urine, blood, skin) were negative, except for respiratory cultures, which were positive for *Stenotrophomonas maltophilia* (104 CFU/ml). Antibiotic susceptibility reports for *S. maltophilia* indicated resistance to TMP/SMX but sensitivity to levofloxacin.

Despite comprehensive and aggressive supportive therapy, the patient's laboratory results deteriorated further: RBC 3 T/L, WBC 1.4 G/L, platelet count 6 G/L, CK 10601 U/L, APTT 103 sec, LDH 763 U/L, CRP 167 mg/L, PCT 1.2 μg/L, and IL-6 2791 ng/L.

The patient's condition deteriorated throughout his ICU stay and he died 30 days after hospital admission.

On autopsy, the only pathological finding was observed in the lungs, which showed signs of hemorrhagic pneumonia (Fig. 2). The presence of Guillain−Barré syndrome was not confirmed.

DISCUSSION

S. maltophilia is an increasingly prevalent nosocomial bacterium, particularly in hospital and intensive care unit settings. It poses a significant risk of opportunistic infections in immunocompromised patients, potentially leading to severe conditions such as bacteremia and pneumonia [3]. A key challenge in managing *S. maltophilia* infections is their nonspecific clinical presentation, often resembling other types of infections. Given the severity and rapid progression of *S. maltophilia* infections, early suspicion and intervention are imperative.

Administration of antibiotics, particularly tigecycline and carbapenem therapy, within 1 month, increases the susceptibility to a *S. maltophilia* infection [1]. Hemorrhagic pneumonia linked to *S. maltophilia* has been reported in individuals with hematological disorders and newborns [2−4]. Several risk factors for hemorrhagic pneumonia caused by *S. maltophilia* in patients with hematological malignancies include advanced age, severe neutropenia (≤ 5 G/l), profound thrombocytopenia (≤ 20 G/l), elevated procalcitonin concentrations, and use of carbapenem antibiotics [3]. Hemorrhagic pneumonia is a relatively common clinical presentation of *S. maltophilia* bacteremia in patients after allogeneic hematopoietic stem cell transplantation [5,7]. To the best of our knowledge, this is the first reported case of hemorrhagic pneumonia caused by *S. maltophilia*, years after kidney transplantation. It shows that *Stenotrophomonas* infection may cause hemorrhagic pneumonia without neutropenia and bloodstream infection.

In our case, the patient exhibited leukocytosis, thrombocytopenia, and a slightly elevated procalcitonin concentration. Notably, concentrations of interleukin-6, C-reactive protein, creatine kinase, lactate dehydrogenase, and potassium all increased rapidly. Leukopenia and severe pancytopenia were detected only shortly (12 hours) before the patient's death. Our case report emphasizes that alongside typical and frequent thrombocytopenia, dyspnea, and characteristic CT changes, notable laboratory warning signs include severe hyperkalemia, elevated concentrations of creatine kinase, lactate dehydrogenase, C-reactive protein, and interleukin-6 may be potential warning signs of hemorrhagic pneumonia caused by *S. maltophilia*.

While high viral copy numbers (EBV, HSV) and acute lower limb paralysis initially suggested Guillain−Barré syndrome, this diagnosis was ultimately ruled out, and the underlying cause of the lower limb weakness was probably caused by hyperkalemia.

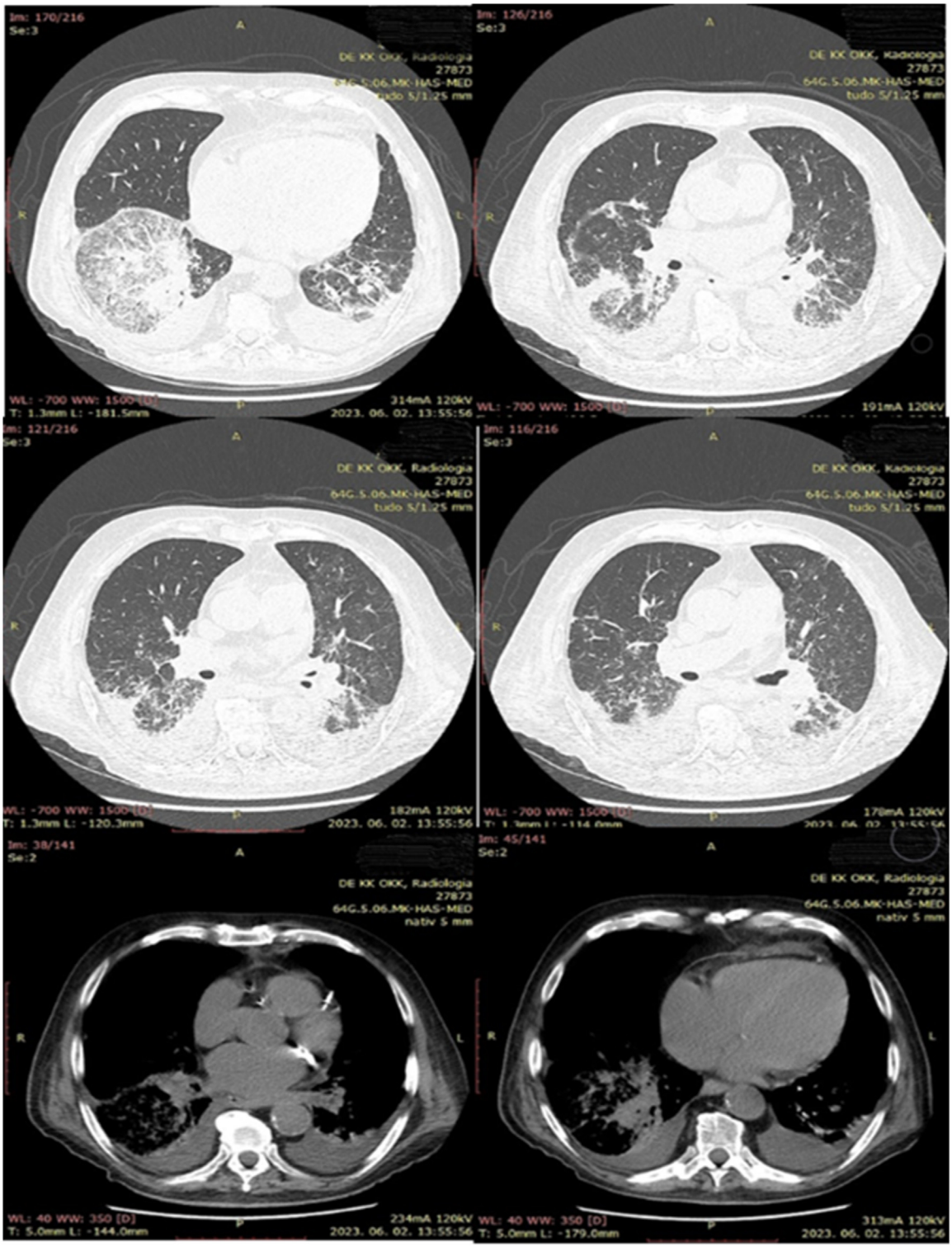

Fig 1. *Stenotrophomonas maltophilia* infection in the lung. Axial chest CT scan: bilateral pleural effusion, ground-glass opacity in the right lower lobe, pericardial effusion.

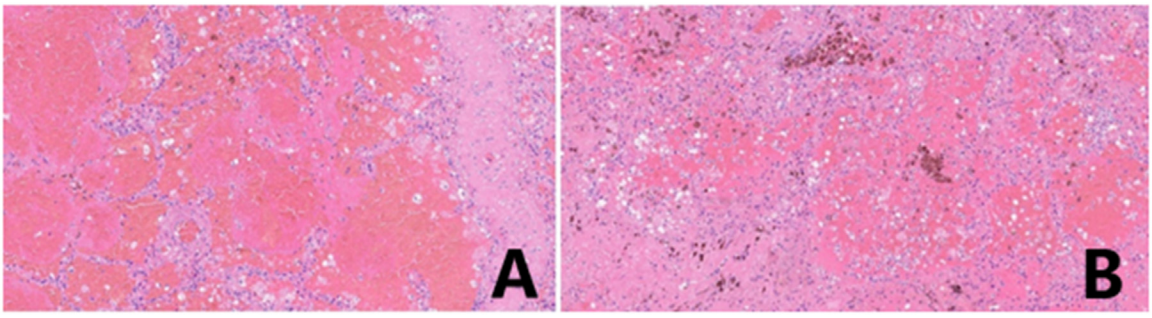

Fig 2. Histological images of *Stenotrophomonas maltophilia* infected lung: **(A)** Multiple alveolar alterations typically characterized by the presence of hyaline membranes within alveolar walls, fibrin deposition, shedding of alveolar cells, and necrosis of type I pneumocytes. (Hematoxylin-eosin staining) **(B)** Mononuclear cells and debris fill the alveoli, and numerous alveoli exhibit the presence of hemosiderin pigment. (Hematoxylin-eosin staining).

While our patient was not treated in intensive care and did not undergo mechanical ventilation, the prolonged use of carbapenem and tigecycline therapy may have contributed to the development of a *S. maltophilia* airway infection.

Although TMP/SMX therapy was promptly initiated after ICU admission, it proved ineffective due to *Stenotrophomonas* strains showing resistance to TMP/SMX and susceptibility to levofloxacin. The patient's respiratory culture results highlight the potential effectiveness of early fluoroquinolone antibiotic therapy when *S. maltophilia* infection is suspected.

Given the rapid and severe nature of the condition and the high incidence of TMP/SMX resistance, timely and appropriate antibiotic treatment is crucial in managing this life-threatening infection.

An important factor was the ticagrelor treatment because this medicine is extensively metabolized by hepatic CYP3A enzymes and may increase the blood levels of everolimus [6]. It is advisable to avoid strong CYP3A inhibitors whenever possible during everolimus treatment, as making compensatory dose reductions of everolimus could pose challenges in management. The patient's medical history, including carotid stent placement, atrial fibrillation, and drug-eluting stents due to coronary restenosis, justified the necessity for antithrombotic therapy. In our case, the increased everolimus blood level may have been caused by ticagrelor treatment, leading to severe immunosuppression. The ticagrelor treatment regimen may have also contributed to the severity of pulmonary hemorrhage, even with a lower *S. maltophilia* bacterial count. The incidence of severe forms of rare nosocomial opportunistic infections may increase with ticagrelor treatment during everolimus immunosuppressive therapy.

DECLARATION OF COMPETING INTEREST

All the authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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