Title: Anti-glomerular basement membrane (GBM) nephritis potentially induced by nebulised tobramycin inhalation

Running title: Anti-GBM nephritis after TOB inhalation therapy

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Abstract

Objective: To describe a case of anti-glomerular basement membrane (GBM) nephritis that occurred shortly after initiation of nebulised tobramycin (TOB) therapy using intravenous solution, suggesting an association with the inhalation therapy and the disease onset.

Background: With the emergence of antimicrobial resistance, clinical importance of aminoglycosides that usually remain susceptibility against gram-negative organisms is increasingly acknowledged. Despite the growing number of evidence supporting the effectiveness of aminoglycoside inhalation therapy for respiratory tract infections, its clinical application has yet to be widely approved by Japanese health insurance.

Case presentation: A 79-year-old Japanese woman had developed amyotrophic lateral sclerosis and experienced recurrent pneumonia mainly caused by *Pseudomonas aeruginosa*, which required monthly treatments with broad-spectrum antibiotics. Due to the limited approval, we had no choice but to use intravenous TOB solution for inhalation therapy as an off-label use under an endorsement of the Institutional Review Board of the hospital. Although the repeated pneumonia subsided, the patient subsequently needed immunosuppressive therapy along with plasma exchanges for the treatment of anti-GBM nephritis.

Conclusion: Although this off-label use of intravenous solutions is common in both clinical and research purposes, our case raised an issue that its safety needs to be re-evaluated.

TEXT

Introduction

In this age of increasing antimicrobial resistance, aminoglycosides remain efficacious against gram-negative organisms and can be selected as a last resort in many clinical cases. Despite their effectiveness, aminoglycosides are often oto- and nephro-toxic, requiring close monitoring of their serum concentrations. Inhalation therapy can achieve a high drug concentration in the alveoli and bronchus without an increase in serum levels. Therefore, aminoglycoside inhalation therapy has been formally approved by authorities for certain respiratory infections such as bronchiectasis, cystic fibrosis, and mycobacterial lung disease [1]. However, nebulisation of the antimicrobial is yet to be established in general practice in Japan, and limited evidence is available regarding its clinical effectiveness and safety [2]. Herein, we describe a case of anti-glomerular basement membrane (GBM) nephritis that occurred shortly after initiation of nebulised tobramycin (TOB) therapy, suggesting its association with the inhalation therapy and disease onset.

Case

A 79-year-old Japanese woman who had been diagnosed with amyotrophic lateral sclerosis experienced recurrent pneumonia. Physical examination revealed decreased chest movement and difficulty in coughing up sputum. Sputum culture identified mucoid-type *Pseudomonas*

aeruginosa, and chest computed tomography demonstrated worsening pneumonia. The patient was treated with various antimicrobials including tazobactam/piperacillin and meropenem; however, *P. aeruginosa* pneumonia recurred and the patient was treated almost monthly (**Fig. 1**). To completely eradicate the recurrent infection, we discussed introducing aminoglycoside inhalation therapy which had not been officially approved by Japanese insurance at that time. Therefore, we submitted a treatment plan for TOB inhalation therapy to the Institutional Review Board of the hospital, using intravenous solution (Towa Pharmaceutical Co., Ltd., Osaka, Japan). After approval of the Board and fully explaining the utility and safety of the drug treatment, we obtained a consent from the patient and initiated the TOB inhalation therapy using an Omron Mesh Nebuliser NE-U200 (OMRON Corporation, Kyoto, Japan) that generates particles with a size of 5 μm (https://store.healthcare.omron.co.jp/nebulizer-net/lineup/compare.html). Since then, *P. aeruginosa* has not been isolated from sputum, and pneumonia has not recurred any more.

Five weeks after commencing inhalation therapy, the patient became feverish. A fever work-up detected granular and erythrocyte casts in urine alongside progressive elevation of serum creatinine level. The serum TOB level at that time was confirmed to be less than lower limit of <0.4 μg/mL. We suspected an acute kidney injury caused by any cause, and tested for anti-nuclear, anti-neutrophil cytoplasmic, and anti-GBM antibodies, and complements. Consequently, anti-GBM antibody tested positive (55.7 U/mL) and

complement 3 level was decreased at 72 mg/dL (normal range, 80-140 mg/dL). The patient did not manifest any symptoms or findings suggestive of alveolar haemorrhage. Although renal biopsy was not performed due to limited medical resources and her underlying neurological disease, the patient was diagnosed with anti-GBM nephritis. Under a tentative diagnosis of TOB inhalation therapy-induced anti-GBM disease, we treated the patient with high-dose corticosteroid, cyclophosphamide, and plasma exchange therapy. Subsequently, the circulating anti-GBM antibody levels declined and renal function returned; however, the patient finally passed away due to difficulty in expectorating sputum three months after the onset of anti-GBM disease.

Discussion

This clinical case suggests the possibility of TOB inhalation therapy triggering anti-GBM disease, although the causality remains to be elucidated. Anti-GBM disease is an immune complex small vessel vasculitis, whose definitive diagnosis should be based on pathological evidence of anti-GBM antibody deposition in the glomerulus or alveoli. The estimated incidence of the disease is reportedly 0.5 to 1 cases per million inhabitants per year, without any significant variation between Asian and Caucasian populations [3]. The disease peaks in people in their thirties and seventies. Due to the rarity of the disease, it is difficult to conclude

that the anti-GBM disease occurred by chance in this case. Rather, we suspect an association between TOB inhalation therapy and anti-GBM disease.

Literature search did not detect any clinical case reports, suggesting our assumption. A high concentration of aminoglycosides in the airway might injure the lung tissue, potentially leading to a hyperimmune response against the basement membrane. However, a previous study demonstrated that a 6-months long administration of TOB inhalation did not cause any clinical or histopathologic changes in dogs compared to the air control, suggesting the safety of TOB inhalation therapy itself [4]. While, the dose of TOB used in our patient could have been responsible for the disease onset. In the literature, however, a common regimen was 300 mg TOB inhalation twice daily [5], which is 2.5 to 5 times higher than the concentration used in our case. Thus, this cannot be a plausible reason as well.

The use of intravenous TOB solution may have been associated with the development of anti-GBR disease. As of March 2021, when we administered the inhalation therapy to the patient, inhalable aminoglycosides available in Japan were TOBI® Podhaler (tobramycin inhalation powder; Novartis Pharmaceuticals Corporation) and ARIKAYCE® (amikacin liposome inhalation suspension; Insmed Incorporated). However, insurance coverage is limited to *P. aeruginosa* respiratory infection in a patient with lung cystic fibrosis for TOBI® and *Mycobacterium avium* complex refractory lung infection for ARIKAYCE®. Therefore, we could not administer these approved drugs to our patient and had to use the

intravenous TOB solution for inhalation. Intravenous TOB solution we used (60 mg per vial) contains sodium hydrogen sulphite (4.8 mg), sodium chloride (4.5 mg), and sulfuric acid (proper quantity) as excipients. Of these, use of sulphites in aerosol preparations were discontinued because of a paradoxical bronchospasm [6]. In this way, intravenous solutions may contain a chemical that should be avoided for aerosol use and we assume that one of these additives could be associated with the disease onset rather than TOB itself. Although this off-label use is now commonly applied to patients worldwide for both clinical and research purposes, our case raised an issue that its safety needs to be re-evaluated.

Aminoglycoside inhalation therapy can cause acute kidney injury as a result of absorption of the aerosolised agent and elevation of its concentration in serum [7]. However, in this case, we confirmed that the serum level of TOB was undetectable and found no such possibility. The presence of intensive renal interstitial and tubular damage suggested by urinalysis was indicative of a condition induced by an inflammatory disease, solely not by an elevation of TOB.

In summary, we described a case of anti-GBM nephritis possibly triggered by the off-label use of intravenous TOB solution for inhalation therapy. The causal relationship between antimicrobial inhalation therapy and anti-GBM disease should be carefully investigated in future study. Additionally, aminoglycoside inhalation therapy is strictly limited to certain diseases in Japan, and clinicians occasionally encounter patients with

trouble in treatment strategies. We advocate for the expansion of the Japanese insurance coverage for existing inhalation products for various respiratory infections.

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186 ***Figure legend***

187 **Figure 1. Clinical course of the case indicating tobramycin (TOB) inhalation therapy-**

188 **induced anti-glomerular basement membrane (GBM) disease.**

189 The patient received TOB inhalation therapy for 2 months from the beginning of March to the

190 end of April. In the first half, 60 mg TOB intravenous solution diluted with 10 mL normal

191 saline was given twice daily, and in the second half, 120 mg TOB diluted with 10 mL normal

192 saline was administered once daily. Following TOB inhalation, the serum creatinine level

193 surged and test for anti-glomerular basement membrane antibody was positive, suggesting

194 rapidly progressive glomerulonephritis. The patient underwent immunosuppressive treatment

195 and 13 rounds of plasma exchange, and her renal function improved. Finally, however, the

196 patient died of respiratory failure due to the underlying amyotrophic lateral sclerosis.

197 Solid and dotted black lines indicate serum creatinine level (left t-axis) and estimated

198 glomerular filtration rate (eGFR, right y-axis), respectively. A gray line with white triangle

199 suggest serum level of anti-GBM antibody (right y-axis). MRSA, methicillin-resistant

200 *Staphylococcus aureus.*