中文題目：散播性諾卡氏菌病在血液疾病患者:革蘭氏染色會有幫助！

英文題目：Disseminated Nocardiosis in a hematologic patient: Gram stain may help!

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Introduction

Nocardiosis which we learned in our microbiology text books, is often forgotten but should not be neglected as it might notify clinicians with morbidity and mortality of patients. Nocardiosis, an opportunistic infection, presents as localized and systemic suppurative disease. Incidence of Nocardia in Taiwan is not clear. It mostly occurs in immunocompromised patients which might confuse clinicians with other organisms causing similar clinical appearance. Culture is the most common and easily done method of diagnosis but is limited by experience and awareness of lab clinicians. Gram stain might give clues to diagnosis if clinicians keep an eye on Nocardia.

Case presentation

A case of 64 years old man with underlying pure red cell aplasia (PRCA) under steroid therapy, post cholecystectomy status for gall stones-associated cholecystitis and type 2 diabetes mellitus under oral anti-diabetic medications has been followed up at out-patient department (OPD) for his PRCA. Follow-up chest X ray in April 2022 showed left upper lung patchy infiltrates which gradually evolved to cavitation in May 2022 (proven in computed tomography, CT). He was hospitalized in July 2022 due to delayed resolution of left upper lung infiltrate. Possible pathogens including mycobacterium, fungus, virus (including cytomegalovirus) and malignancy were checked and discharged home with antibiotics use. Mycobacterium kansasii was isolated and medications targeted for NTM was used since August 2022.

Due to breathlessness, he was hospitalized again on August 3, 2022 and intubated for respiratory distress. At that time, COVID-19 test showed positive and so he was cared in isolation ward. Intravenous Remdesivir and dexamethasone for COVID-19 infection were prescribed according to Taiwan CDC guideline. His vital signs on

admission were as follows: body temperature of 38'C, blood pressure 119/90mmHg, pulse rate 128/min, respiratory rate 30/min, pulse oximeter 95% with venturi-mask 15L/min(FiO2 60%). Lab tests were as follows: hs-CRP 28.66mg/dl, d-dimer 14,073.7 ng/ml, ferritin >15,000ng/ml, procalcitonin 24.86 ng/ml, total bilirubin 5.01mg/dl, WBC 9.8x10^3/ul, Hb 8.2g/dl, platelet 102x10^3/ul.

CT chest and abdomen on August 6, 2022 showed hypodense lesions in liver and lungs and suspected abscesses or septic emboli. Empirical use of cefepime, levofloxacin and teicoplanin for severe community acquired pneumonia with suspected lung abscess and liver abscess was done for immunocompromised patient. Later, cefepime was switched to meropenem for better coverage. Cytopenia was treated with supportive care, like transfusion and injection of colony-stimulating factor. Percutaneous abscess drainage of liver abscess was once planned but canceled due to difficult approach and high risk of complications. Nocardia bacteremia was noted on day 5 and adjusted antibiotics to amoxicillin-clavulanic acid and then to amikacin due to impairment of liver function. Sputum culture performed on Day 2 and day 18 yielded Candida albicans and Candidemia due to Candida albicans was detected on day 12. Fluconazole was used initially and then shifted to anidulafungin due to liver function impairment. Nocardia was isolated from sputum of day 4 and sulfamethoxazole-trimethoprim was added. Carbapenem resistant Klebsiella pneumoniae bacteremia was noted on day 17. Dexamethasone 4mg QD was kept for underlying PRCA. NTM medications were held since admission due to liver impairment. Carbapenem resistant Acinetobacter baumanii was noted on sputum of day 20 and IV and inhaled colistin was used.

Brain CT was done on day 21 showed brain abscess formation at left posterior temporal-parietal-occipital region and abutting to left lateral ventricle trigone with mild suspected mass effect. Patient's family refused operation for brain abscess. After discussion with infection specialist, conservative treatment with Meropenem + Amikacin + Linezolid for nocardiosis with multiple abscesses formation.

Tracheostomy was suggested for chronic ventilator use with high risk of ventilator associated pneumonia, but refused to do so. On Day 33, family decided for hospice care and natural course with no more blood tests, antibiotics use, vasopressor use, transfusion and dialysis. He expired on 48th day of hospitalization.

In this patient, even early noticing the gram stain appearance of branched bacilli or weakly acid fast bacilli, overwhelming disseminated infection of Nocardia was

intimidating for him. That's why early recognition of risk factors for some pathogens and how to diagnose them can contribute to the entire clinical outcome.

Discussion:

Nocardiosis, which is suppurative infection by Nocardia, class: Actinobacteria, order: Actinomycetales, family: Nocardiaceae, can be local or systemic infections in immunocompetent hosts but for immunocompromised hosts, it can be fatal without proper treatment. Nocardia species found are plants, gardens and soil in the environment. Of more than 80 species, human diseases are caused by more than 50 species. Among these, Nocardia brasiliensis is a predominantly found species in Taiwan. Clinical features are similar to other pulmonary infections. Chest radiographs manifestation might be variable, presenting with nodular lesions, cavitation or delayed resolution of pneumonia patch.

Culture was the commonest and easiest way to diagnose, but also mostly missed reports due to longer time for growth and overlooked for extended incubation period. Prior antibiotics use before sampling culture might also interfere with sensitivity. Gram staining or acid fast staining like modified Ziehl-Neelsen or Kinyoun stain can also be used. However, NTM might interfere with acid fast stain as they might coexist in similar patient groups. Other modalities like PCR (16S r-RNA based polymerase chain reaction) and metagenomic next-generation sequencing (mNGS) for earlier identification of Nocardia are now available but not widely used, due to limitations, like clinicians' suspicion to test for PCR and high cost for mNGS. The most efficient way to improve diagnosis might be gram staining and suspicion by clinicians, when there is risk of infection. Early awareness and referral of isolates to a reference laboratory, should be considered in high risk patients with high suspicion when no other ways for diagnosis. Treatment of nocardiosis is individualized and species orientated as blind try or even empirical use might fail when some nocardiae with species-specific susceptibility profiles, and commonly multi-drug resistance. Sulfonamides (trimethoprim-sulfamethoxazole, TMP-SMX) were used as part of first line therapy. Linezolid, tigecycline, amikacin and carbapenem are also used in nocardiosis. Combination therapy may be first considered until the patient becomes more clinically stable. Even with susceptible agents, patients might fail to respond to therapy. Proper antibiotics for at least 3-6 months and even 6-12 months in serious or immunocompromised patients is recommended due to relapsing nature of

nocardiosis. Surgical intervention or drainage may be needed in suppurative lesions with poor response to medications. Poor prognosis is anticipated in Nocardia bacteremia with disseminated lesions.

Conclusion:

Nocardiosis, well-known for disseminated abscess formation in multiple sites, has similar clinical features to those of atypical pneumonia and tuberculosis, as chronic wasting and indolent features. Nocardiosis reminds clinicians, not to forget some uncommon pathogens. Gram staining of specimens which only takes a few minutes might help early diagnosis and possibly change the clinical outcome of patients.