Infections and Treatment Journal

Sequential Diagnosis of Pneumococcal Pneumonia, Thyroid Storm, Cytomegalovirus Colitis and Invasive Pulmonary Aspergillosis in A Patient with Graves' disease

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Abstract

We report the 67 years old man of Graves' disease with invasive pulmonary aspergillosis after prolonged stay in the intensive care unit due to sequential development of pneumonia caused by *Streptococcus pneumoniae*, thyroid storm and *Cytomegalovirus* colitis. Antifungal therapy was not given in time before death. The glucocorticoid therapy could facilitate the *Cytomegalovirus* infection, which might also be associated with the subsequent development of aspergillosis.

Key words

Aspergillosis; Cytomegalovirus; Colitis; Graves' disease; Thyroid storm

Introduction

Invasive pulmonary aspergillosis (IPA) could occur after prolonged hospitalization in the intensive care unit (ICU). We report a delayed recognition of infection caused by *Aspergillus* in a patient with pneumococcal sepsis-induced thyroid storm on prolonged course of glucocorticoid therapy, which then predisposed to *Cytomegalovirus* (CMV) colitis. Prolonged ICU stay, glucocorticoid therapy and CMV infection all are risk factors for the further development of IPA.

Case Report

A 67 years old man of Graves' disease without regular follow-up presented with progressive dyspnea for 2 weeks. Productive cough and bilateral leg edema were noted in recent 3 days. There was no fever, diarrhea, or skin rash. The patient visited the hospital on October 19, 2015. Laboratory data showed a white blood cell (WBC) count of 5,500/μL; C-reactive protein (CRP), 8.1 mg/L (normal, <6); procalcitonin (PCT), 12.8 ng/mL (normal, < 0.05); lactate, 6.2 mmole/L (normal, 0.4-2.0); aspartate aminotransferase, 360 U/L (normal, 5-34); alanine aminotransferase, 183 U/L (normal, 2-40); total bilirubin, 3.09 mg/dL (normal, 0.2-1.2); direct bilirubin, 2.18 mg/dL (0.1-0.5); creatinine, 2.21 mg/dL; HbA1C, 6.5% and albumin, 3.9%.

The initial chest x-ray (CXR) film showed cardiomegaly, lung congestion and bilateral pleural effusions (Figure 1A). Influenza A and B rapid antigen screen and polymerase chain reaction (PCR) for influenza A (H1N1) virus in nasopharyngeal swab samples all showed negative results. Urine *Pneumococcus* rapid screen test was positive, whereas urine *Legionella* antigen test was negative. An N-terminal pro-brain natriuretic peptide (NT-proBNP) of 5943 pg/mL (normal, <125) was noticed. Together with electrocardiogram showing atrial fibrillation with rapid ventricular response, pneumococcal sepsis-induced thyroid storm with congestive heart failure was suspected. An initial blood culture did not reveal any growth, while sputum culture yielded few cefazolin-susceptible *Klebsiella pneumoniae*.

Thyroid function tests included a free tetraiodothyronine of 2.32 ng/dL (normal, 0.70-1.48); anti-thyroglobulin, 6.6 IU/mL (normal, <5); anti-thyroid peroxidase, 10.0 IU/mL (normal, <5); a thyroid-stimulating hormone (TSH) level of 0.03 μIU/mL (normal, 0.25-4.0); and TSH receptor-Ab, 60.6% (normal, <14). Echocardiography revealed global hypokinesia and poor left ventricular (LV) systolic function with a LV ejection fraction ranging from 19% to 28%. Treatment consisted of propylthiouracil, Lugol's iodine (2%) solution, hydrocortisone, dopamine, propranolol, digoxin, furosemide and an antibiotic of piperacillin-tazobactam. His lung condition became markedly improved (Figure 1B). A follow-up WBC count of 8,600/μL and a PCT of 1.59 ng/mL were noted on Oct. 29, 2015.

However, fever and bloody stool occurred 2 weeks later. The colorectal examination by colonoscopy revealed a huge recto-sigmoid colon ulcer on November 4 (Figure 2). The

Article Information

DOI: 10.31021/ITJ.20191103
Article Type: Case Report
Journal Type: Open Access
Volume: 1 **Issue:** 1
Manuscript ID: ITJ-1-103
Publisher: Boffin Access Limited

Received Date: 29 March 2019
Accepted Date: 15 April 2019
Published Date: 17 April 2019

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Citation: Ku YH, Yang CC, Yu WL. Sequential diagnosis of pneumococcal pneumonia, thyroid storm, cytomegalovirus colitis and invasive pulmonary aspergillosis in a patient with graves' disease. Infect Treat J. 2019 Apr;1(1):103

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histopathology of tissue biopsy confirmed CMV colitis. Meanwhile, CMV antigenemia was 5 positive cells per 200,000 macrophages and CMV viral load was 6,530 IU/mL. A PCR assay for CMV DNA in the stool sample was positive. Meanwhile, the blood screening for *Aspergillus* antigen of galactomannan index was 0.24 (normal, <0.5). Ganciclovir was added for CMV colitis since November 11, 2015.

In addition, a sputum culture obtained on November 9 yielded *Pseudomonas aeruginosa* and antibiotic was shifted to ciprofloxacin with good therapeutic results. During the 4th week of hospital stay; however, *Aspergillus* species was isolated from sputum culture obtained on November 16, 2015. Meanwhile, shock occurred and a CXR film showed nodular patches over left lung field (Figure 1C). A PCT level increased to 8.69 ng/mL and CRP became 35.7 mg/L. A blood culture obtained on November 16 yielded ciprofloxacin-resistant *Escherichia coli*. A blood sample for *Aspergillus* antigen obtained on November 17 became an index of >5.16. As severe and

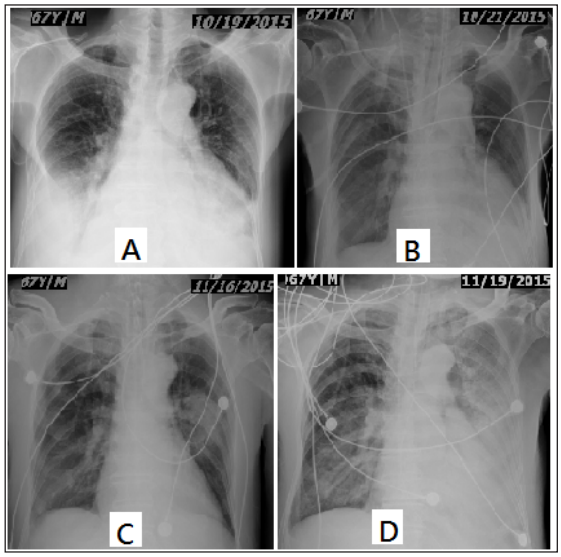

Figure 1: CXR films show lung congestion and bilateral pleural effusions on October 19, 2015 (A), which is markedly improved on Oct. 21 (B); left-sided nodular patches on November 16 (C), which rapidly progressed to extensive consolidation on November 19, 2015 (D)

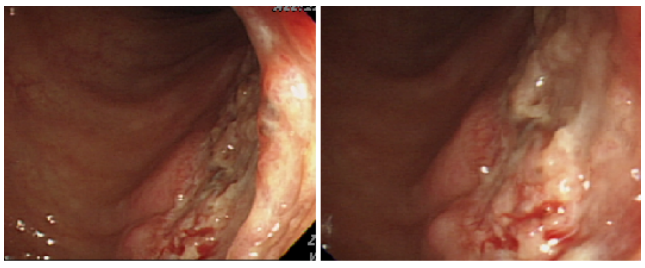

Figure 2: Examination of colonoscopy reveals a huge ulcer from rectum (at 8 cm from the anal verge) to sigmoid colon (at 16 cm from the anal verge)

refractory septic shock and worsening pneumonia (Figure 1D), the patient died on November 19, 2015. Appropriate antibiotics and antifungal therapy were not given in time before death.

Throughout the whole course of hospitalization, the patient had been on hydrocortisone therapy (300 mg/day for 5 days, followed by 150 mg/day for 5 days, 100 mg/day for 8 days, 50 mg/day for 8 days, then at last 100 mg/day for 6 days). Lymphopenia

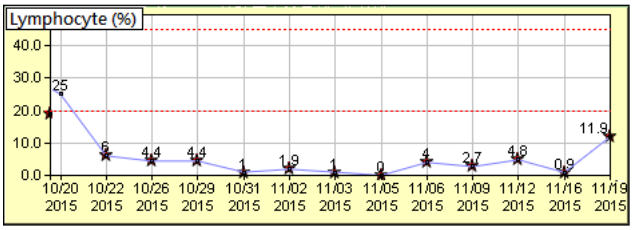

Figure 3: Lymphopenia (<1,000/μL) had been noted for most of time during hospitalization

(<1,000/μL) had persisted for most of time during hospital stay (Figure 3).

Discussion

Diagnosis of thyroid storm in our reported patient was mainly based on thyrotoxicosis combined with congestive heart failure, arrhythmia, and hepatic disturbances [1]. Infection is one of several risk factors predisposing to thyroid storm [2,3]. The high levels of PCT and lactate as well as positive urine pneumococcal screen test suggested the presence of sepsis in our patient. Prompt initiation of anti-thyroid and antibiotic therapy resulted in rapid improvement.

Management of thyroid storm includes a multimodality treatment, such as propylthiouracil, glucocorticoids, beta-blockers, and monitoring in an ICU [4]. Nonetheless, reactivation of latent CMV infection may occur in previously immunocompetent critically ill individuals [5]. In addition, glucocorticoids are transcription factors that facilitate the transcription of CMV to reactivation [6]. Therefore, prolonged steroid use and stay in the ICU are the most commonly associated risk factors for CMV disease in our patient.

However, worsening pneumonia occurred during 4th week after admission, as the occurrence of *Aspergillus* in the sputum culture and positive *Aspergillus* antigen assay in the blood, which rapidly progressed to fatal pneumonia. Even though an earlier screening for blood *Aspergillus* antigen assay after 2 weeks of hospitalization was negative during CMV reactivation, it highlights that CMV itself is also a precipitating factor for late-onset IPA. CMV reactivation has been reported to be an independent risk factor for invasive fungal disease among transplant recipients undergoing solid organ and allogeneic hematopoietic stem cell transplantation [7,8]. Host genetic Toll-like receptor polymorphisms and low CD3 lymphopenia are likely to be contributory factors for invasive aspergillosis [7,9]. Therefore, persistent lymphopenia in our patient with CMV disease may hint the need to continuously consider the development of IPA even in the late stage of the course.

Conclusion

In conclusion, our case highlights invasive *Aspergillus* infection following CMV colitis, which might be reactivated by prolonged hydrocortisone use for thyroid storm. Our patient reminds physicians that potential co-infections of CMV and aspergillosis cannot be overemphasized.

Ethical Approval

The study and waiver from the inform consent process were approved by the Institutional Review Board (IRB) of the Chi Mei Medical Center, Tainan city, Taiwan (IRB Serial number 10801-002).

Conflict of Interest

The authors declare that they have no financial support and competing interests.

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