# Hong Kong College of Physicians
# Case report for Interim Assessment
# Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

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| Name of candidate (print and sign): |
| Hospital and Unit: Specialty: |
| Name of supervisor (print and sign): |
| Date(s) and place (hospital) of patient encounter: **11 Feb 2021** |
| Date of report submission: **10 Mar 2021** |

## Case report

**Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.**

**Title: Pneumocystis pneumonia while on steroid and rituximab for pemphigus vulgaris**

**Case history:**

A 45-year-old woman presented with fever for 1 week when she was clinically admitted for her 7th dose of weekly rituximab infusion for pemphigus vulgaris.

The patient noted on and off fever since 1 week ago, with chills, myalgia and occasional dry cough, but no shortness of breath. She had no abdominal, urinary or neurological symptoms.

The patient enjoyed good past health until 9 months ago, when she started to have generalized blisters all over her body. Skin biopsy confirmed the diagnosis of pemphigus vulgaris around 3 months ago, and oral prednisolone was started since then. She was initially on prednisolone 60mg daily, which was gradually tapered down to 25mg daily one week before this admission. She was recruited into a clinical trial for pemphigus vulgaris 2 months ago, and was given 2 courses of monthly intravenous immune globulin (IVIg) of 2g/kg/course and 6 doses of rituximab (375 mg/m2 of body surface, once weekly) before this admission. Pre-trial workup confirmed negative results for hepatitis B virus antigen (HBsAg), anti-hepatitis B core (HBc) antibody, anti-hepatitis C virus (HCV) antibody, anti-human immunodeficiency virus (HIV) antibody, and interferon-gamma release assays (IGRA) for tuberculosis (TB) and a clear chest x-ray. Her skin condition was slowly

improving in the past few weeks.

The patient was an ex-smoker who quitted 15 years ago. She was married with 1 daughter. She was born in Sichuan and came to Hong Kong in 2003. She was working as a porter in a private hospital, and had no recent travel history. She denied any personal or family history of tuberculosis. She had no known drug allergy. Other than oral prednisolone 25mg daily, she was on oral calcium and vitamin D, pantoprazole and topical steroid before this admission.

On examination, the temperature was 38°C, with normal blood pressure and pulse rate, and oxygen saturation of 97% on room air. Examinations over her respiratory, cardiovascular, abdominal and neurological systems were all normal. She had no palpable lymph nodes, and her calves were soft. She had inactive generalized skin lesions from her pemphigus without active inflammation or discharge, and had no active oral ulcers.

On admission, the white blood cell count was 10.21 x 10^9/L (normal, 3.89-9.93) with a high neutrophil count of 9.20 x 10^9/L (normal, 2.01-7.42), low lymphocyte count of 0.81 x 10^9/L (normal, 1.06-3.61) and low eosinophil count of 0.00 x 10^9/L (normal, 0.02-0.45). Serum electrolytes, creatine kinase, as well as the liver and kidney function tests were normal. C-reactive protein (CRP) was high at 3.47mg/dl (normal, <0.76). Chest x-ray was clear.

The patient was started on intravenous amoxicillin-clavulanate on admission, and rituximab infusion was withheld. Blood procalcitonin level was <0.1 mcg/L, indicating bacterial sepsis was unlikely. Filmarray multiplex polymerase chain reaction (PCR) assays using her nasopharyngeal swab and sputum were negative for common respiratory bacteria and viruses. Urine routine was not suggestive of infection. Bloods for cytomegalovirus pp65 antigen and cryptococcal antigen were negative.

The patient had persistent swinging fever up to 39°C, mild cough with minimal mucoid sputum. She had no desaturation on room air, and her white blood cell counts and CRP level remained static. Urine, sputum and repeated blood cultures all returned negative for routine bacteria. Sputum and early morning urine were negative for acid-fast bacilli smear and TB-PCR. Screening autoimmune markers were negative, while completement and serum immunoglobulin levels were normal. On hospital day 3, oral doxycycline 100mg twice daily was added while amoxicillin-clavulanate was stopped, as there is no evidence of pyogenic infection. Prednisolone was reduced to 20mg daily on hospital day 6 according to dermatological plan.

On hospital day 7, fever persisted and the patient reported minimal shortness of breath in the morning. Serial chest x-rays showed mild bilateral diffuse lung infiltrates. Blood lymphocyte count gradually rose from 0.81 x 10^9/L to 1.01 x

10^9/L. Serum lactate dehydrogenase (LDH) was elevated at 368 U/L (normal, 107-218). On day 8, sputum came back positive for Pneumocystis jiroveci PCR. Blood glucose-6-phosphate dehydrogenase (G6PD) level was normal. Oral cotrimoxazole (trimethoprim-sulfamethoxazole) 1680mg three times daily was started for presumed Pneumocystis pneumonia (PCP). Although the patient remained stable on room air, prednisolone was stepped up to 40mg daily for 5 days to prevent paradoxical reaction in view of recovering lymphocyte count.

In view of persistent fever, a positron emission tomography and computerized tomography (PET-CT) scan of the whole body was done on hospital day 11, which showed bilateral hypermetabolic lung consolidation, centrilobular nodules and diffuse ground glass opacities more around the bronchovasculature, compatible with atypical pneumonia. Echocardiogram showed normal ejection fraction and valves with no vegetation seen. Subsequent serology for Brucella, Bartonella and Q fever all came back negative.

The patient remained stable on room air, and fever completely subsided after 9 days of cotrimoxazole. 3-week course of cotrimoxazole was initially planned for the treatment of PCP for the patient, but she developed generalized maculopapular rash after 10 days of cotrimoxazole use. Allergy to cotrimoxazole was labelled and she was switched to primaquine 30mg daily plus clindamycin 450mg four times daily to complete the remaining 11 days of treatment.

CRP and LDH normalized upon completion of antibiotics. Prednisolone was further stepped down gradually according to dermatological plan. Monthly nebulized pentamidine prophylaxis was arranged for secondary PCP prophylaxis. Outpatient follow-up was arranged, and rituximab was planned to be resumed only after the infiltrates on chest x-ray completely clear up.

## Discussion and literature review

This case described a middle aged woman who developed Pneumocystis pneumonia (PCP) while on tapering steroid and rituximab for pemphigus vulgaris. This case highlighted few issues regarding PCP which deserve in-depth discussions.

First of all, traditionally CD4+ T lymphocytes are pivotal in host defense against pneumocystis. However, use of systemic steroid alone, without underlying immunodeficiency or use of other cytotoxic agents, rarely cause PCP [1]. In our case, a potential predisposing factor for PCP might be the concurrent use of rituximab, an anti-CD20 monoclonal antibody which depletes B cells, though the role of B cells in fighting against PCP infection remains unclear. In a retrospective study of 30 patients who received rituximab and developed PCP between 1998 and 2011, though 73 percent of them received systemic steroid together with rituximab, 10 percent of them did not have concomitant chemotherapy or significant glucocorticoid exposure, supporting the association between rituximab and PCP [2]. In this case, the patient was particularly vulnerable, as she was on moderate to high-dose steroid for more than 2 months, and a rather intensive trial regimen of rituximab without any PCP prophylaxis.

Classically, PCP patients present with fever and respiratory insufficiency. However, our patient presented with swinging fever for a week, minimal cough with no dyspnea at all. Her chest x-ray was also clear until hospital day 5. In a retrospective study of 614 patients with PCP, with 143 being HIV-positive and 461 being HIV-negative, HIV-negative patients presented significantly less frequently with cough ($p = 0.0003$) and dyspnea ($p < 0.00001$) compared to HIV-positive patients, while fever was similarly prevalent in both groups. Asymptomatic presentation of PCP (with positive radiological findings) was significantly ($p = 0.009$) more frequent in HIV-negative patients [3]. In our case, sputum was sent for pneumocystis PCR only on hospital day 7 and tested positive on day 8. This delay might be because of minimal cough, a lack of desaturation and a clear chest x-ray on admission. It may be prudent to always consider PCP as one of the differentials for persistent fever even if cough or dyspnea is absent, especially in an HIV-negative patient who is on tapering steroid and another immunosuppressant.

Moving onto diagnosis, the gold standard of PCP diagnosis is by identifying pneumocystis with microscopy and staining of an induced sputum or bronchoalveolar lavage fluid, as pneumocystis cannot be cultured [1]. Nowadays, quantitative polymerase chain reaction (PCR) platforms have shown excellent sensitivity of >99% for PCP, even though the specificity may be lower (90-94%), especially when used on BAL, due to the inability to differentiate between infection and colonization [4]. Notably, To et al. (2013) reported high sensitivity and

specificity of 100% and 96.1% respectively when using quantitative PCR on nasopharyngeal aspirate for diagnosis of PCP in Hong Kong [5]. In our patient, the microbiological diagnosis of PCP was only presumptive as her sputum was only tested positive for pneumocystis PCR, which may be due to colonization instead of infection. However, considering her risk factors, clinical and radiological findings, and subsequent improvement with cotrimoxazole, a diagnosis of PCP should be certain.

For treatment of PCP, cotrimoxazole (trimethoprim–sulfamethoxazole) for 3 weeks remains the first line regimen, but its use may be limited by side effects such as rash (as in our case) mostly due to sulfonamide allergy, myelosuppression, hyperkalemia and hemolysis in patients with G6PD deficiency. Second-line options include primaquine plus clindamycin, intravenous pentamidine, and atovaquone (for mild disease only) [6]. Primaquine is also contraindicated in G6PD deficiency. In a large observational study of 1122 HIV-infected PCP patients, 7% of patients switched from first line to second line therapy due to treatment failure and 17% of patients did so due to intolerance. Compared with cotrimoxazole, multivariable cox regression analysis revealed a significantly higher risk of death with pentamidine (hazard ratio 3.3, 95% CI = 2.2–5.0) but not with primaquine plus clindamycin [7]. Therefore, primaquine plus clindamycin should be chosen over pentamidine whenever possible (as in our patient), unless in cases with severe G6PD deficiency. Notable side effects of the former including methemoglobinaemia and Clostridium difficile colitis must also be watched out [8].

The benefit of adjunctive corticosteroid treatment in HIV-positive patients with moderate to severe PCP is well proven from meta-analysis [8]. However, no high quality studies have been carried out in HIV-negative patients to date, while observational studies had conflicting results. In a recent retrospective study on 139 HIV-negative, hypoxaemic PCP patients admitted into Intensive Care Unit, high dose steroid treatment was an independent predictor of mortality but was not associated with increased risk of infection [9]. Although confounding factors and bias cannot be excluded from a retrospective study, use of adjunctive corticosteroid in HIV-negative patients should be cautious and individualized. In our patient who was already on slowly tapering steroid treatment before onset of PCP, the risk of developing significant paradoxical inflammatory reaction should be low, and hence maintaining the current steroid dosage or slightly escalating the dose briefly (as in our case) would likely be sufficient. Future randomized clinical trials are needed to define the best approach for these patients.

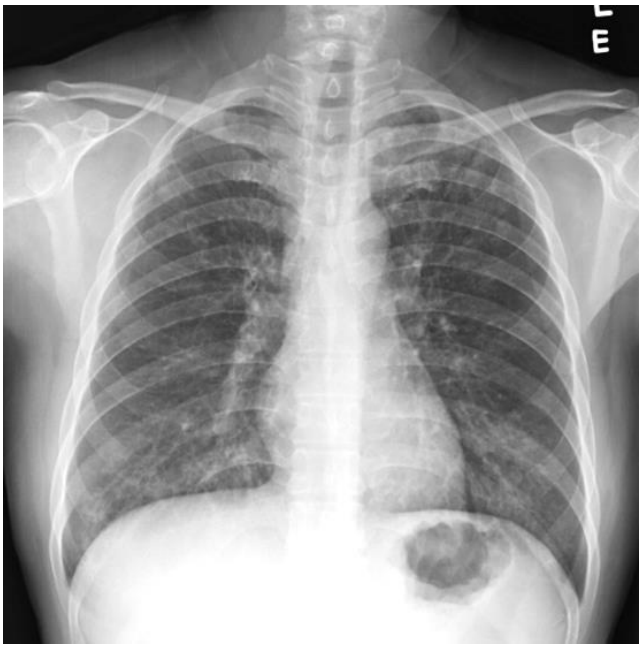
After the completion of PCP treatment, our patient must be kept on secondary prophylaxis, which would be inhaled pentamidine as she had rash with cotrimoxazole. However, monthly inhaled pentamidine was shown to be associated

with more breakthrough PCP cases than cotrimoxazole when used as prophylaxis in randomized trials, and thus pentamidine should not be used as first line prophylaxis [8]. When to stop the secondary prophylaxis in those with recovering immune system is not well defined in the literature, but in our case, should at least be 6 months after completion of steroid and rituximab, if not longer.

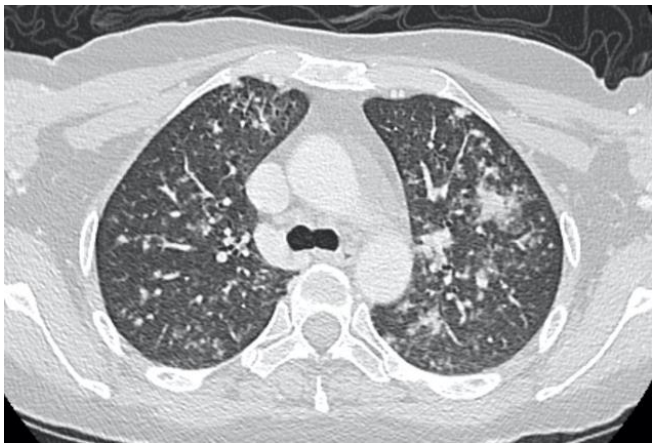
Whether or not future patients on prolonged steroid plus rituximab should be given primary PCP prophylaxis remains undetermined. International guideline has only recommended PCP prophylaxis for patients with haematological malignancies being put on prolonged steroid or rituximab-based chemotherapy [10], while there are no guidelines regarding PCP prophylaxis on rheumatological patients receiving immunosuppressants. After all, the risk of PCP in patients without underlying immunodeficiency and being put on immunosuppression is considered low, and the decision on primary PCP prophylaxis should best be individualized.

In conclusion, this case illustrated a typical case of opportunistic infection with Pneumocystis pneumonia, which may see a rise amid the rapid development of potent immunosuppression with monoclonal antibodies. While routine prophylaxis may not be the go-to approach for all patients, heightened vigilance, prompt and accurate diagnostic techniques, effective treatment options together with targeted secondary prophylaxis, should minimize any harm even when such infection unfortunately sets in.

**Tables and figures** (where applicable) (no more than two figures)



Chest x-ray on hospital day 7 showing bilateral lung infiltrates



Computed tomography of chest on hospital day 11 showing bilateral lung consolidation and diffuse ground glass opacities

**Reference** (not more than 10)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Transplantation (EBMT), the European Organisation for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and the European LeukemiaNet (ELN). ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016 Sep;71(9):2397-404.

**No of words in Case History and Discussion (excluding references):_____1980_____**

**(should be between 1000-2000)**

## Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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