Case Report

Methemoglobinemia in an HIV-Infected Patient Treated with Primaquine for *Pneumocystis jirovecii* Pneumonia

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Case : A 38-year-old male patient with HIV infection developed cyanosis and slight dyspnea during the treatment for *Pneumocystis jirovecii* pneumonia with primaquine (30 mg/day). Since the methemoglobin level of the patient's blood was as high as 11.3% on the tenth day of primaquine administration, we diagnosed his condition as methemoblobinemia. Ten days after the cessation of primaquine treatment, the patient's methemoglobin level fell to 1.1%.

Discussion : Iatrogenic methemoglobinemia can confound the diagnosis of diseases that cause dyspnea and cyanosis such as *Pneumocystis jirovecii* pneumonia.

Key words：methemoblobinemia, primaquine, HIV, *Pneumocystis jirovecii* pneumonia

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Introduction

Pneumocystis jirovecii pneumonia (PCP) is common in patients with acquired immunodeficiency syndrome (AIDS). Trimethoprim-sulfamethoxazole (TMP-SMX) is the first choice for treating PCP ; the alternatives are pentamidine and atovaquone. Primaquine combined with clindamycin is another choice when patients respond poorly or have toxic reactions to other agents[1, 2]. We herein report a case of an HIV-positive male patient who developed a decline in his oxygen saturation by pulse oximeter (SpO_2) during treatment for PCP and was diagnosed with primaquine-induced methemoglobinemia.

Case Report

A 38-year-old Japanese man presented with a three-month history of dyspnea, malaise and appetite loss, and a one-month history of chest pain and high fever. He was admitted to a local hospital and was diagnosed with PCP and AIDS. The initial CD4 T-cell count was 51 cells/μL and HIV-RNA 1,200,000 copies/mL. He immediately began receiving TMP-SMX and prednisolone for PCP, and transferred to our hospital on the eighth day for further examination and treatment. TMP-SMX was discontinued after ten-day use because the patient developed hyponatremia (Na 119 mEq/L) and hyperkalemia (K 5.5 mEq/L). As second-line treatment, the patient received pentamidine, which was discontinued five days later due to elevated serum creatinine levels and glucose intolerance. As third-line treatment, the patient received atovaquone.

Despite pentamidine and atovaquone administration, chest radiographs indicated a worsened condition since the discontinuation of TMP-SMX. On hospital day 19, when atovaquone was discontinued after three-day administration, the patient began receiving primaquine 30 mg/day (0.58 mg/kg/day) and clindamycin, after confirming the normal level of the glucose-6-phosphate dehydrogenase (G6PD).

Although his chest radiographs revealed an improvement of PCP after five-day treatment with primaquine and clindamycin, the patient gradually developed slight exertional dyspnea. General examination and radiological images were unremarkable, except for subtle cyanosis of the lips and nail beds. Pulse oximetry displayed a decline in SpO_2.

On the tenth day of primaquine and clindamycin therapy, arterial blood gas analysis showed a partial pressure of oxygen (PaO_2) of 198 mmHg while his SpO_2 was 92%, receiving oxygen at 3 L/min via a nasal cannula. His arterial blood appeared relatively dark (Fig. 1). On testing, the methemoglobin level was 11.3%, which demonstrated that he had methemoglobinemia. Because his PCP on radiological findings made a good recovery, primaquine and clindamycin were discontinued on the very day. Methylene blue was not used as treatment for

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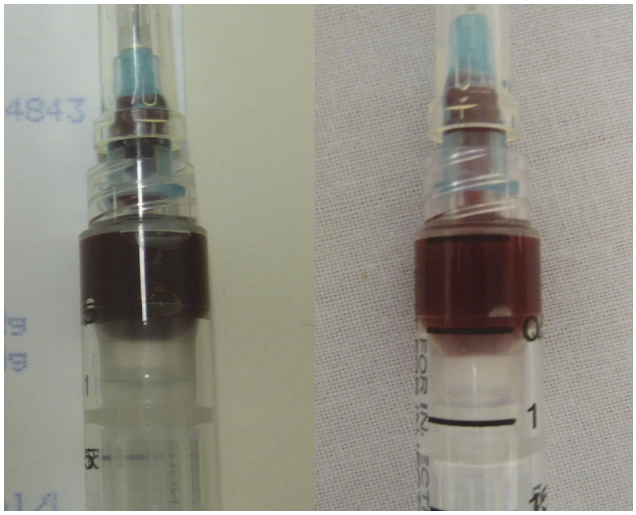

Figure 1 Comparison of arterial blood.
The patient's darkened blood showing methemoglobinemia (left) and normal blood of another adult (right).

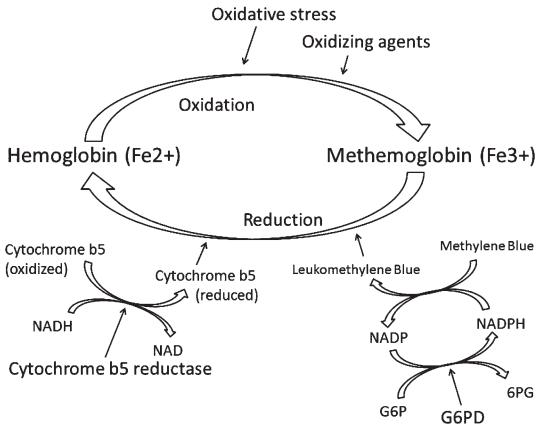

Figure 2 Mechanisms of oxidation of hemoglobin and reduction of methemoglobin, including methylene blue treatment pathway.
NAD, nicotinamide adenine dinucleotide ; NADP, nicotinamide adenine dinucleotide phosphate ; G6P, glucose-6-phosphate ; 6PG, 6-phosphogluconate ; G6PD, glucose-6-phosphate dehydrogenase. Adapted from References (3, 4, 8).

methemoglobinemia. PCP was assumed to be cured and the secondary prophylactic dose of TMP-SMX was initiated the next day. Hyponatremia, hyperkalemia and other side effects did not develop.

Ten days after the cessation of primaquine and clindamycin, the methemoglobin level fell to 1.1% without any additional treatment. Anti-retroviral therapy using tenofovir disoproxil fumarate, emtricitabine, and raltegravir was started eleven days after PCP treatment finished.

Laboratory tests performed later revealed a normal level in his NADH-cytochrome b5 reductase.

Discussion

Our patient developed a decline in SpO_2, mild cyanosis and dyspnea during treatment for PCP and AIDS. The differential diagnoses included PCP treatment failure, pneumothorax, bacterial pneumonia, viral pneumonia, pulmonary embolus, or cardiac diseases, all of which were disconfirmed by physical or radiologic findings. We were led to the diagnosis of methemoglobinemia by distinct signs and the drug history : a "saturation gap" (the discrepancy between SpO_2 and PaO_2), asymptomatic cyanosis, blood darkening and primaquine use.

Methemoglobinemia is an increase in methemoglobin, wherein the ferrous ions of normal hemoglobin are oxidized to the ferric state by oxidative stress or oxidizing agents (Fig. 2). Methemoglobin has low oxygen-carrying capacity. This in turn causes tissue hypoxia[3,4].

Blood oxygen levels are usually evaluated by consulting blood gas analysis-derived PaO_2 and pulse oximetry-derived SpO_2. In methemoglobinemia, PaO_2 is high while SpO_2 is low because pulse oximetry only measures the absorbance of light which correspond to oxyhemoglobin and deoxy-hemoglobin. When methemoglobin, which has different absorbance from oxyhemoglobin and deoxy-hemoglobin, increases in blood, pulse oximeter displays relatively low SpO_2[3~5]. That also explains asymptomatic cyanosis and blood darkening.

Normal levels of methemoglobin in adults are below 1%. Cyanosis and discoloration of blood may occur when the methemoglobin level is over 10%. Much higher levels can cause dyspnea, headache, deteriorating consciousness, and in worst cases, death[3,4].

Congenital methemoglobinemia results from a defect in hemoglobin metabolism-related enzymes such as NADH-cytochrome b5 reductase or G6PD, while acquired methemoglobinemia is related to use of various medicines or chemicals including primaquine, dapsone, sulfa antibiotics, local anesthetics, nitrates, or metoclopramide[3,4].

Primaquine is a well-known antimalarial agent, which has been reported to cause methemoglobinemia during the treatment of malaria[6] and PCP[7~9]. Higher dose of primaquine can increase the risk of methemoglobinemia, but therapeutic doses of primaquine rarely cause severely symptomatic or life-threatening cases[6].

In Japan, since it has been nationally unlicensed drug, primaquine has been seldom used and there have been few reports discussing primaquine-induced adverse events including methemoglobinemia. A retrospective analysis on 94 Japanese patients with *Plasmodium vivax* and *Plasmodium ovale* malaria treated with primaquine, in

which 48 cases were treated with 15 mg/day for 14 days and 37 cases treated with 30 mg/day for 14 days, reported a few cases of liver dysfunction and abdominal pain but no case of methemoglobinemia[10].

What made our patient develop methemoglobinemia was unclear. He developed mild methemoglobinemia of 11.3% of methemoglobin in blood after receiving 30 mg/day of primaquine for 10 days. He had neither G6PD deficiency nor NADH-cytochrome b5 reductase deficiency. The important factor in our successful diagnosing the patient's condition was that he had been hospitalized and under treatment of PCP, a disease potentially causing respiratory malfunction. We had paid careful attention to his signs and symptoms, which may have enabled us to recognize his slight cyanosis and examine his methemoglobin levels. Close examination of methemoglobin levels in blood among Japanese patients receiving primaquine is necessary to reveal the accurate incident rates of primaquine-induced methemoglobinemia.

To treat methemoglobinemia, suspected toxic agents must be removed from the system first. Oxygen administration is generally performed. Intravenous methylene blue administration (1−2 mg/kg) can be considered when the patient is symptomatic[3,4]. Methylene blue is reduced to leucomethylene blue, and in turn reduces methemoglobin to normal hemoglobin (Fig. 2).

The findings of this case indicate that iatrogenic methemoglobinemia can confound the diagnosis of diseases that cause dyspnea and cyanosis such as PCP.

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Conflicts of interest : None of the authors have any conflicts of interest to declare.

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プリマキンによる HIV 合併ニューモシスチス肺炎治療中にメトヘモグロビン血症を来たした 1 例

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症例：ニューモシスチス肺炎（PCP）で AIDS 発症した 38 歳の男性。PCP に対する標準的治療により副作用が出現したためプリマキン 30 mg/日とクリンダマイシンの併用療法を行っていたが，チアノーゼとわずかな呼吸苦が出現し，経皮的動脈血酸素飽和度（SpO_2）が低下した。プリマキン投与 10 日目の血中メトヘモグロビン値が 11.3% と上昇していたため，メトヘモグロビン血症と診断した。被疑薬であるプリマキンを中止して保存的治療を行ったところ，10 日後には血中メトヘモグロビン値は 1.1% に低下した。

考察：原因不明の呼吸苦，チアノーゼ，SpO_2 低下等を見たときは，メトヘモグロビン血症を疑う必要がある。

キーワード：メトヘモグロビン血症，プリマキン，HIV，ニューモシスチス肺炎