INTERNAL⬤MEDICINE

Methemoglobinemia Induced by Trimethoprim-Sulfamethoxazole in a Patient with Systemic Lupus Erythematosus

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Abstract

We herein report a case of methemoglobinemia induced by trimethoprim-sulfamethoxazole (TMP/SMX). A 41-year-old woman with systemic lupus erythematosus (SLE) received TMP/SMX for prophylaxis of pneumocystis pneumonia (PCP) on the 7th day of hospitalization. She suddenly developed dyspnea and cyanosis on the 9th day of hospitalization. The level of oxygen saturation (SaO$_2$) decreased, and the concentration of methemoglobin (MetHb) in the blood was elevated. We diagnosed the patient with methemoglobinemia induced by TMP/SMX. Methemoglobinemia should be considered in cases of sudden dyspnea following TMP/SMX administration.

Key words: methemoglobinemia, trimethoprim-sulfamethoxazole, systemic lupus erythematosus

Introduction

Methemoglobinemia can be hereditary or acquired. Some drugs oxygenate iron in the hemoglobin molecule, interfering with the ability to carry oxygen and inducing acquired methemoglobinemia. This disease is difficult to diagnose due to its rarity. A diagnosis of intercurrent methemoglobinemia should be considered in patients with a high arterial oxygen pressure (PaO$_2$) in spite of the presence of dyspnea or cyanosis.

Case Report

A 41-year-old woman with no family history of methemoglobinemia was admitted to the hospital for the treatment of acute cardiac failure. Because she developed acute kidney injury (AKI), nephrotic syndrome and thrombotic microangiopathy (TMA), she was transferred to our hospital for management of the clinical complications. We diagnosed the patient with systemic lupus erythematosus (SLE) because she satisfied five of the 11 criteria [serositis, a renal disorder, hematologic disorders (hemolytic anemia, leukopenia, lymphopenia), an immunologic disorder (positivity for anti-double-stranded DNA antibodies and anti-Sm antibodies) and a high titer of antinuclear antibodies] for the classification of SLE (1). We immediately administered steroid pulse therapy (methylprednisolone: 1,000 mg/day, three days), intravenous cyclophosphamide therapy (500 mg/m^2 body surface area), cyclosporine (200 mg/day), plasma exchange therapy and continuous hemodiafiltration. The clinical manifestations related to TMA gradually improved.

Prior to the administration of trimethoprim-sulfamethoxazole (TMP/SMX), the methemoglobin (MetHb) level was below 1%. On the 7th day of hospitalization, we administered TMP/SMX (TMP 80 mg, SMX 400 mg) for prophylaxis against pneumocystis pneumonia (PCP). The patient's respiratory condition was stable with the use of nasal high-flow therapy, and on the 7th day, her readings were as follows: PaO$_2$: 100.5 mmHg, arterial carbon dioxide pressure (PaCO$_2$): 26.8 mmHg, oxygen saturation (SaO$_2$): 99.2% and MetHb: 1.9%. However, she suddenly developed dyspnea and cyanosis on the 9th day of hospitalization. The SaO$_2$ decreased to 94.7%, while the MetHb increased to 5.7%. On
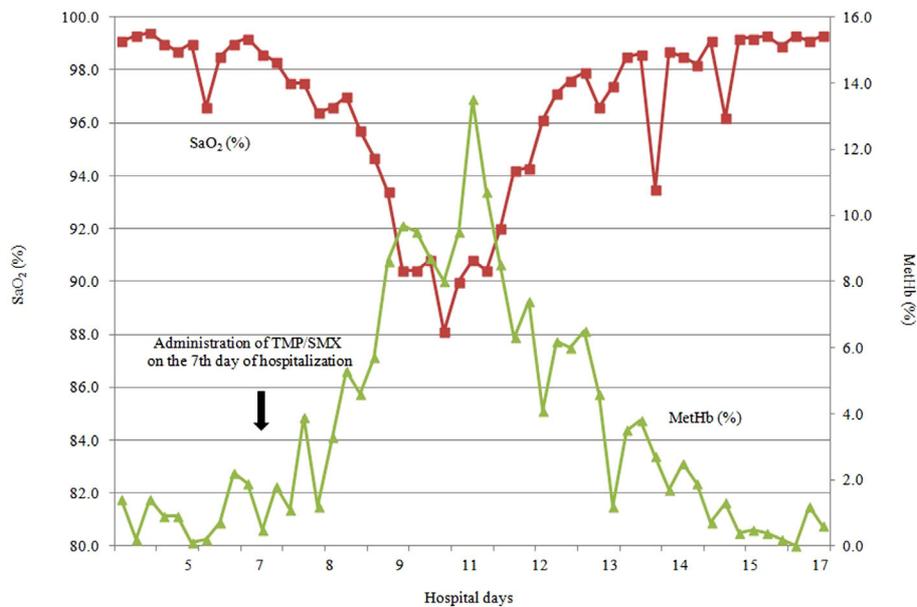
Figure. We administered TMP/SMX (TMP 80 mg, SMX 400 mg) only once on the 7th day of hospitalization. On the 11th day of hospitalization, the MetHb level was markedly elevated to 13.5% (SaO$_2$: 90.8%). Following the discontinuation of TMP/SMX, the MetHb level returned to within the normal limits on the 15th day of hospitalization (SaO$_2$: 99.2%, MetHb: 0.4%). SaO$_2$: oxygen saturation, MetHb: methemoglobin, TMP/SMX: trimethoprim-sulfamethoxazole

the 11th day of hospitalization, the dyspnea worsened (PaO$_2$: 217.3 mmHg, PaCO$_2$: 29.6 mmHg, SaO$_2$: 90.8%), and the MetHb level was markedly elevated at 13.5%. We believed that the cause of the methemoglobinemia was the administration of TMP/SMX because similar cases had been previously reported (2). TMP/SMX was administered only once. Following the discontinuation of TMP/SMX, the MetHb level returned to within the normal limits on the 15th day of hospitalization (SaO$_2$: 99.2%, MetHb: 0.4%; Figure).

Discussion

SLE is a systemic autoimmune disease characterized by facial erythema, autoimmune-induced cytopenia, nephritis and neuropsychiatric involvement. The first-line treatment has traditionally been high doses of corticosteroids, which act as potent suppressors of autoimmunity. Various infections by bacteria, viruses and fungi are problematic in patients with corticosteroid-treated SLE. Infection is responsible for approximately 25% of all deaths in SLE patients, making it a leading cause of mortality in this population (3, 4). The prevalence of life-threatening infections appears to be highest within the first five years of SLE onset (3, 5). PCP is a common infection in immunocompromised hosts. TMP/SMX is often administered in patients receiving immunosuppressant therapy for prophylaxis of PCP. In Japan, PCP has been reported to be an important cause of mortality in SLE patients on long-term immunosuppressant therapy. However, following the administration of TMP/SMX, the frequency of PCP is typically diminished. In contrast, TMP/SMX is known to have many adverse ef-

fects, including methemoglobinemia (2).

A common feature of methemoglobinemia is a high PaO$_2$ despite a rapid decrease in SaO$_2$. A patient can be diagnosed with methemoglobinemia based on a high MetHb percentage. Cyanosis, as observed in our patient, is typically associated with a MetHb level >10%-20%; a MetHb level >50% is often associated with respiratory failure, an altered mental status and other neurological symptoms (6).

Methemoglobinemia occurs when the production of MetHb exceeds its removal. TMP/SMX, dapsone, lidocaine, benzocaine, prilocaine, acetaminophen, nitroprusside, phenazopyridine and zopiclone have been reported to cause acquired methemoglobinemia (2, 7, 8). In our patient, no drugs, except TMP/SMX, were administered that were known to cause methemoglobinemia.

The pathogenic mechanisms underlying the development of TMP/SMX-associated methemoglobinemia are not well understood. Sulfamethoxazole and dapsone are both arylamine compounds that generate similar hydroxylamine metabolites that lead to adverse drug reactions, and both drugs are metabolized by the N-acetyl transferase 2 (NAT2) and cytochrome b5 (cyt b5)/NADH cytochrome b5 reductase (b5R) pathways (9, 10). A case of dapsone-associated methemoglobinemia with an *NAT2*5B* haplotype has been reported (11). Furthermore, slow NAT2 genotypes have been reported to be risk factors for dose-dependent adverse reactions to sulfasalazine (12). We originally believed that there was an association between the NAT2 slow acetylator genotype and susceptibility to methemoglobinemia. However, our case involved the NAT2 rapid acetylator type. Further work is needed to determine whether the *NAT2*5B* haplotype con-

fers a risk for methemoglobinemia.

Clinical risk factors associated with methemoglobinemia include renal failure (13), sepsis, gastrointestinal infection (14) and decreased glucose-6-phosphatase dehydrogenase (G6PD) activity (15). G6PD is necessary to generate NADPH, which otherwise maintains an adequate glutathione concentration within erythrocytes and counteracts hemoglobin oxidation. Patients with G6PD deficiency are at increased risk of oxidative stress due to reduced glutathione concentrations. Exogenous oxidizing agents can then overwhelm the cyt b5/b5R system, leading to increased production of MetHb (16). The level of G6PD in our patient was not determined.

We considered another pathogenic mechanism in our case: the cyt b5/b5R-catalyzed reduction of heme iron. Congenital methemoglobinemia is induced by a deficiency in b5R. However, a very low level of cyt b5/b5R reduction activity was reported in the leukocytes of an acquired methemoglobinemia patient (11). The patient in that study exhibited a low leukocyte messenger RNA (mRNA) expression for *CYB5A* (which encodes cyt b5) and *CYB5R3* (which encodes b5R) compared with healthy controls, consistent with the patient's low reduction activity. Cyt b5/b5R also catalyzes the reduction of sulfamethoxazole hydroxylamine. Kurian et al. reported that polyclonal antibodies to cyt b5/b5R significantly inhibit the reduction of sulfamethoxazole hydroxylamine (9). It is unclear whether anti-b5R antibodies were produced in our case. However, the possibility of this phenomenon cannot be denied because a variety of antibodies are produced in patients with SLE. Alternatively, the b5R activity can be decreased via other mechanisms. In such situations, reduction of the level of heme iron may be competitively inhibited by the administration of TMP/SMX.

Sulfhemoglobinemia is difficult to distinguish from methemoglobinemia (17). Sulfhemoglobinemia involves alteration of the hemoglobin porphyrin ring and develops in association with cyanosis and dyspnea due to the use of drugs, such as TMP/SMX. Cyanide or newer co-oximetry machines are needed to distinguish these diseases. In our case, a diagnosis of sulfhemoglobinemia could not be ruled out.

The treatment for acquired methemoglobinemia includes the discontinuation of suspicious drugs and the administration of intravenous or oral methylene blue. In our case, the patient's dyspnea improved and the MetHb percentage decreased following the discontinuation of TMP/SMX. We did not initiate methylene blue treatment because MetHb did not reach a dangerous level.

To our knowledge, our report is the first of methemoglobinemia occurring in a patient with SLE. Furthermore, TMP/SMX-associated methemoglobinemia has not been previously reported in Japan. In Japan, TMP/SMX is often administered to patients receiving immunosuppressive therapy for PCP prophylaxis. A diagnosis of methemoglobinemia should be considered in cases of sudden low SaO$_2$ following TMP/SMX administration.

The authors state that they have no Conflict of Interest (COI).

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