Isontiazid-induced Pure Red Cell Aplasia in a Patient with Sarcoidosis: A Patient Summary and Review of the Literature

Yasuyuki Saito¹, Yuri Sawada¹, Yasuhiko Koga¹, Noriaki Sunaga¹,², Yusuke Tsukagoshi¹, Yoshimasa Hachisu¹, Takashi Osaki¹, Reiko Sakurai¹, Kyoichi Kaira¹, Akihiro Ono¹, Ken Sato¹, Hiromi Koiso⁴, Tetsunari Oyama⁵, Takeshi Hisada¹ and Masanobu Yamada¹

Abstract:
A 41-year-old woman treated with isoniazid (INH) for latent tuberculosis infection and an oral corticosteroid for sarcoidosis developed severe anemia two months after initiating INH. A bone marrow examination showed erythoblastopenia, and a diagnosis of INH-induced pure red cell aplasia (PRCA) was made. Her reticulocyte count and hemoglobin levels improved two weeks after discontinuation of INH. A literature review of INH-induced PRCA shows that it occurs very rarely in the context of autoimmune disorders. This report describes a case of INH-induced PRCA occurring in a patient with sarcoidosis.

Key words: isoniazid, pure red cell aplasia, sarcoidosis, autoimmune disorders, latent tuberculosis infection, biological drug

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Introduction

The routine treatment of active tuberculosis and latent tuberculosis infection (LTBI) has increased with the availability of biological drugs. The side effects of anti-tuberculosis drugs include various hematologic side effects. Reports indicate that isoniazid (INH) causes eosinophilia, leukocytosis, neutropenia, thrombocytopenia, autoimmune hemolytic anemia, pure red cell aplasia (PRCA), and sideroblastic anemia. PRCA is a rare complication caused by the disruption of hematopoiesis by INH. Secondary PRCA can be induced by viral infections, anti-erythropoietin antibodies, thymoma, chronic lymphocytic leukemia, pregnancy, drugs, and autoimmune disorders such as rheumatoid arthritis (RA), myasthenia gravis (MG), mixed connective tissue disease (MCTD), and systemic lupus erythematosus (SLE) (1). PRCA is characterized by erythoblastopenia, with otherwise normal bone marrow production. Severe PRCA is associated with a marked decrease in the number of reticulocytes and the absence of erythroblasts in bone marrow. Drugs such as procainamide, sulfa, diphenylhydantoin, amide drugs, ticlopidine, allopurinol, penicillamine, azathioprine, and ribavirin can induce PRCA (1), but <5% of all cases of PRCA are drug-induced. INH is also reported to induce secondary PRCA, and there have been two studies describing Asian patients with INH-induced PRCA (2, 3). Furthermore, cases of autoimmune disorders exacerbated by INH-induced PRCA are very rare; this is the first case report of a patient with sarcoidosis. The observations should be considered by clinicians managing patients on anti-tuberculosis treatment.
Sputum cultures were negative for Mycobacterium tuberculosis, and there was no evidence of active pulmonary tuberculosis on computed tomography (CT). We diagnosed the patient with LTBI. To prevent inducing an active case of tuberculosis due to the use of oral corticosteroid therapy, INH treatment for LTBI was started one week after the initiation of PSL.

Approximately three months later at a routine follow-up visit, the patient reported the recurrence of exertional dyspnea starting several weeks prior. A laboratory analysis showed a hemoglobin level of 5.9 g/dL, a reticulocyte count of 2,000/μL (0.1%), and unchanged thrombocytopenia secondary to splenomegaly and chronic liver dysfunction (Table 1). Iron, vitamin B12, and folic acid levels were normal. CT, esophagastroduodenoscopy, and colonscopy showed no evidence of worsening interstitial pneumonia or internal bleeding. A bone marrow evaluation confirmed a significant decrease in the number of erythroblasts, with a high myeloid:erythroid ratio (206:1), but no cell dysplasia (Figure A and B). There was no evidence suggesting any other collagen disease, malignant tumor, or infections such as infectious mononucleosis or erythema infectiousum. The patient had no fever, exanthema, or arthralgia, and none of her family members had infections such as infectious mononucleo-

### Case Report

A 41-year-old woman, who had been followed-up for non-B, non-C, non-alcoholic chronic hepatitis, presented with increased exertional dyspnea and thus was hospitalized. The diagnosis was worsening interstitial pneumonia by sarcoidosis, and she was started on prednisolone (PSL) 20 mg/day. Sarcoidosis had been diagnosed two years prior, when she had presented with pulmonary manifestations of sarcoidosis. At that time, she had had elevated angiotensin-converting enzyme and γ-globulin levels and a negative tuberculin skin test result. During the current admission, an interferon-gamma release assay (IGRA) revealed positive results. Sputum cultures were negative for Mycobacterium tuberculosis, and there was no evidence of active pulmonary tuberculosis on computed tomography (CT). We diagnosed the patient with LTBI. To prevent inducing an active case of tuberculosis due to the use of oral corticosteroid therapy, INH treatment for LTBI was started one week after the initiation of PSL.

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### Table 1. Laboratory Data.

| Blood cell count          | Biochemistry                   |
|---------------------------|--------------------------------|
| White blood cells 4,200/μL| Total bilirubin 1.5 mg/dL      |
| Neutrophils 81.1%         | AST 35 IU/L                    |
| Lymphocytes 13.9%         | ALT 29 IU/L                    |
| Eosinophils 1.2%          | LDH 283 IU/L                   |
| Basophils 0%              | ALP 131 IU/L                   |
| Monocytes 3.8%            | γ-GTP 27 IU/L                  |
| Red blood cells 166×10⁴/μL| Total protein 6 g/dL           |
| Hemoglobin 5.9 g/dL       | Albumin 3.1 g/dL               |
| Hematocrit 16.9%          | Blood urea nitrogen 13 mg/dL   |
| MCV 101.8 fl              | Creatinine 0.49 mg/dL          |
| MCH 35.5 pg               | Sodium 137 mEq/L               |
| MCHC 34.9%                | Potassium 4 mEq/L              |
| Platelets 5.4×10⁴/μL      | Chloride 104 mEq/L             |
| Reticulocyte count 2,000/μL| Calcium 8.1 mg/dL             |
|                          | Serum iron 240 μg/dL           |
|                          | UIBC 13 μg/dL                  |

| Infection                |                                 |
|--------------------------|---------------------------------|
| Parvovirus B19 PCR <100 copy/mL| Ferritin 557.1 ng/mL          |
| EBV                      | Vitamin B12 408 pg/mL          |
| EA IgG (+)               | Folic acid 6 mg/mL             |
| EBNA IgG (+)             | Serology                       |
| VCA IgG (+)              | CRP 0.3 mg/dL                  |
| VCA IgM (-)              | Rheumatoid factor <10 IU/mL    |
| Mumps                    | Anti-nuclear antibody 20 Index  |
| IgM (-)                  | Coagulation                    |
| Neutralizing antibody (+)| APTT 31 second                 |
|                          | PT-INR 1.07                    |

**MCV**: mean corpuscular volume, **MCH**: mean corpuscular hemoglobin, **MCHC**: mean corpuscular hemoglobin concentration, **CRP**: C-reactive protein, **PCR**: polymerase chain reaction, **EBV**: Epstein-Barr virus, **EA**: early antigen, **EBNA**: EBV nuclear antigen, **VCA**: virus capsid antigen, **AST**: aspartate transaminase, **ALT**: alanine transaminase, **LDH**: lactate dehydrogenase, **ALP**: alkaline phosphatase, **γ-GTP**: γ-glutamyl transferase, **UIBC**: unsaturated iron binding capacity, **APTT**: activated partial thromboplastin time, **PT-INR**: prothrombin time-international normalized ratio

- **APTT**: Activated Partial Thromboplastin Time
- **PT-INR**: Prothrombin Time International Normalized Ratio
- **MCH**: Mean Corpuscular Hemoglobin
- **MCHC**: Mean Corpuscular Hemoglobin Concentration
A dose of PSL was decreased, and no other medication count had increased, and the anemia had improved. The blood cell transfusion. Two weeks later, the reticulocyte weeks was thus terminated, and the patient received a red infection. The administration of INH 250 mg/day for 10 presumed that the PRCA was induced by INH, not by a vi-

gas erythema infectiosum. Furthermore, viral infections caused by parvovirus, mumps, and Epstein Barr virus were excluded by viral DNA and antibody tests. We therefore presumed that the PRCA was induced by INH, not by a vi-
rinal infection. The administration of INH 250 mg/day for 10 weeks was thus terminated, and the patient received a red blood cell transfusion. Two weeks later, the reticulocyte count had increased, and the anemia had improved. The dose of PSL was decreased, and no other medication changes were made. We diagnosed this patient with INH-induced PRCA complicated by sarcoidosis. More than one year, the patient has remained well, with stable sarcoidosis and no recurrence of PRCA.

Table 2. Case Reports of Isoniazid-induced Pure Red Cell Aplasia.

| Case No. | Reference No. | Age | Sex | Duration of exposure (months) | Days Recovery (Days) | Coombs test | Dosage of isoniazid (mg) | Other drugs | Transfusion | Hb (g/dL) | Reticulocyte (%) | Complications |
|----------|---------------|-----|-----|-------------------------------|----------------------|-------------|--------------------------|-------------|-------------|-----------|----------------|---------------|
| 1        | 8             | 32  | M   | 6                             | 6                    | (+)         | 750                      | PAS, Pyr, Insulin | (+)         | 4.1       | 0.1         | Type 1 diabetes mellitus |
| 2        | 11            | 42  | M   | 4.5                           | 11                   | (-)         | 300                      | EB, Pyr, PB     | (+)         | 5.5       | 0.2         | Mental retardation          |
| 3        | 11            | 66  | F   | 4                             | 35                   | NR          | NR                      | Pyr, PSL       | (+)         | 7.7       | 0.1         | Thalassemia                  |
| 4        | 11            | 53  | M   | 6                             | 30                   | (-)         | 300                      | Pyr           | (+)         | 6.9       | 0.1         | (-)                      |
| 5        | 11            | 81  | M   | 2                             | 4                    | (-)         | 300                      | EB, Pyr        | (+)         | 6.8       | 0.2         | COPD                     |
| 6        | 12            | 62  | M   | 4                             | 30-45                | (-)         | 300                      | Pyr, PSL       | (-)         | 9         | 0.2         | (-)                      |
| 7        | 12            | 72  | M   | 6                             | 60                   | NR          | 300                      | RFP, ASP       | (+)         | 11.7      | NR          | Arrhythmia                |
| 8        | 9             | 77  | M   | 3                             | 14                   | NR          | 300                      | EB, Pyr, SM    | (+)         | 5         | 0.1         | (-)                      |
| 9        | 13            | 47  | M   | 1.5                           | 22                   | (+)         | 300                      | RFP, EB, PRZ   | (+)         | 7.7       | 0          | (-)                      |
| 10       | 14            | 7   | M   | 9                             | 45                   | (-)         | 12mg/kg                  | (-)           | (+)         | 3.6       | 0           | Liver dysfunction        |
| 11       | 10            | 7   | F   | 6                             | 15                   | NR          | 15mg/kg                  | Pyr           | (+)         | 6         | NR          | (-)                      |
| 12       | 10            | 6   | M   | 7                             | 14                   | NR          | 15mg/kg                  | Pyr           | (-)         | 6         | NR          | (-)                      |
| 13       | 15            | 79  | F   | 1.5                           | 10                   | (-)         | 150                      | RFP, EB, Pyr   | (-)         | 6.3       | 1           | (-)                      |
| 14       | 2             | 47  | F   | 1                             | 119                  | NR          | 200                      | PSL, TAC       | (+), CyA     | 5.8       | NR          | MG, SLE                   |
| 15       | 3             | 34  | F   | 6                             | 14                   | NR          | 250                      | PSL           | (+)         | 5.9       | 0.1         | Sarcoidosis               |

PAS: para-amino salicylic acid, Pyr: Pyridoxine, EB: ethambutol, PB: Phenobutonite, NR: not reported, PSL: prednisone, COPD: chronic obstructive pulmonary disease, RFP: rifampicin, ASP: aspirin, SM: streptomycin, PRZ: pyrazinamide, TAC: tacrolimus, CyA: cyclosporin A, MG: myasthenia gravis, SLE: systemic lupus erythematosus

Figure. Bone marrow histology of a patient with isoniazid-induced pure red cell aplasia. The bone marrow showed marked erythroid hypoplasia with a decreased number of erythroblasts. Bar=20 μm.

Discussion

INH-induced PRCA is a very rare form of drug-induced PRCA, with only 16 cases reported since 1964 (Table 2). This is the first case report of a patient with sarcoidosis in the English language literature. Two cases occurring in Asian patients were reported by Nakamura et al. in 2010 (2) and Shukla et al. in 2014 (3). No influence of race or ethnicity on the onset of PRCA was found. In the present case, an oral corticosteroid was initiated for the treatment of worsening sarcoidosis, with the concomitant use of INH for LTBI. Secondary PRCA associated with autoimmune disorders such as RA, MG, MCTD, and SLE has been re-
ported (4). However, very little has been reported about sarcoidosis and PRCA. Hematopoietic complications are very rare in sarcoidosis. We found two articles describing PRCA in association with sarcoidosis. In one, the patient was diagnosed with parvovirus B19-induced red blood cell aplasia and thrombocytopenia (5). In the other, sarcoidosis was complicated by red blood cell aplasia and malakoplakia (6). Evidence of a direct association between PRCA and sarcoidosis was not found in these cases, nor was it noted in the present case. INH has been shown to induce PRCA. The patient in the present case showed improvement after the discontinuation of INH. Notably, in our case, PSL was started one week prior to starting INH, suggesting that pretreatment with PSL might not have a protective effect against the development of INH-induced PRCA.

Whether or not the exacerbation of sarcoidosis requiring corticosteroid therapy affected the pathogenesis of INH-induced PRCA in our case is unclear. Mizobuchi et al. suggested that a T-cell mediated immunologic response might be associated with the pathogenesis of secondary PRCA (7). Collagen diseases such as RA and SLE are thought to be associated with PRCA. However, the relationship between PRCA and sarcoidosis remains obscure. Additional studies of drug-induced PRCA in the presence of autoimmune disorders are required to elucidate the mechanism of INH-induced PRCA.

In 16 previous reports of INH-induced PRCA (Table 2), the sex ratio was 10:6 (male:female), and the average age of onset was 47.1 years, with a wide age distribution (from infants to elderly adults). Blood transfusion was required in >80% of cases with INH-induced PRCA because the mean period of INH intake prior to the diagnosis was approximately 4.4 months (Table 3); therefore, anemia had progressed to an average hemoglobin level of <7.0 g/dL in patients on long-term anti-tuberculosis therapy. However, transfusion may not be mandatory, but may rather depend on the health status of the patient. Most cases of INH-induced PRCA improved after the discontinuation of INH alone, except for one case with underlying MG and SLE (2). In three cases, INH was re-administered; PRCA recurred in all three cases (8-10). In the case of the patient with MG and SLE, cyclosporine A was added to the existing treatment of PSL; this patient had a longer period of recovery from PRCA (119 days) (2) than the other 15 patients.

Table 3. Patient’s Demographics.

| Variables       | n=16 |
|-----------------|------|
| Age (year)      | Median (range) 47 (6 - 79) |
| Gender          | male / female 10 / 6 |
| Duration of exposure (months) | 4.4 |
| Recovery days (Days) | 29.1 |
| Coombs test     | + / - 2 / 7 |
| Transfusion     | Yes / No 13 / 3 |
| Lowest Hb       | g/dL 6.4 |
| Lowest reticulocyte % | 0.2 |

In recent years, the increased use of biological preparations has increased the need for anti-tuberculoc treatment, including treatment of LTBI. Furthermore, with medical advances, various targeted molecular therapies have been developed, suggesting an even greater need for anti-tuberculosis treatment. Therefore, the use of INH monotherapy for the treatment of LTBI, as in the present case, is expected to increase. It is therefore important to make physicians aware of INH-induced PRCA.

In summary, INH-induced PRCA presents approximately 4.4 months after starting INH. The average hemoglobin level at the diagnosis is 6.4 g/dL, as discovery often happens late. Notably, PRCA recurred in all three cases in which INH was re-administered, suggesting that this practice should be avoided.

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

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References

1. Thompson DF, Gales MA. Drug-induced pure red cell aplasia. Pharmacotherapy 16: 1002-1008, 1996.
2. Nakamura H, Okada A, Kawakami A, et al. Isoniazid-triggered pure red cell aplasia in systemic lupus erythematosus complicated with myasthenia gravis. Rheumatol Int 30: 1643-1645, 2010.
3. Shukla A, Mishra S, Jain M, Tripathi AK. Pure red cell aplasia: a rare complication of isoniazid therapy. Indian J Hematol Blood Transfus 30: 36-37, 2014.
4. Fisch P, Handgretinger R, Schafer HE. Pure red cell aplasia. Br J Haematol 111: 1010-1022, 2000.
5. Viallard JF, Parrens M, Hermine O, et al. Severe prolonged red cell aplasia and thrombocytopenia induced by parvovirus B19 infection in a patient with sarcoidosis. Clin Infect Dis 36: 229-233, 2003.
6. Montero J, Urrutia M, Parra T, Pino A. Testicle malakoplakia associated to aplastic anemia and cutaneous sarcoidosis. Actas Urol Esp 1: 227-230, 1977.
7. Mizobuchi S, Yamashiro T, Nonami Y, et al. Pure red cell aplasia and myasthenia gravis with thymoma: a case report and review of the literature. Jpn J Clin Oncol 28: 696-701, 1998.
8. Goodman SB, Block MH. A case of red cell aplasia occurring as a result of antituberculous therapy. Blood 24: 616-623, 1964.
9. Lewis CR, Manoharan A. Pure red cell hypoplasia secondary to isoniazid. Postgrad Med J 63: 309-310, 1987.
10. Maresgilla GL, Locatelli F. Isoniazid-induced pure red cell aplasia in two siblings. J Pediatr 132: 898-900, 1998.
11. Hoffman R, McPhedran P, Benz EJ, Duffy TP. Isoniazid-induced pure red cell aplasia. Am J Med Sci 286: 2-9, 1983.
12. Claiborne RA, Dutt AK. Isoniazid-induced pure red cell aplasia. Am Rev Respir Dis 131: 947-949, 1985.
13. Johansson R, Lonn M. A case of isoniazid-induced red cell aplasia. Respir Med 84: 171-174, 1990.
14. Velea KS, Huf EF, Nelson BK, Coffman DS. Pure red cell aplasia and hepatitis in a child receiving isoniazid therapy. J Pediatr 120: 146-148, 1992.
15. Loulgue P, Mir O, Dhote R. Pure red blood cell aplasia and isoniazid use. Emerg Infect Dis 13: 1427-1428, 2007.

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