[CASE REPORT]

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

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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 erythroblastopenia, 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 erythroblastopenia, 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.

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Table 1. Laboratory Data.

Blood cell count		Biochemistry	
White blood cells	4,200 / μ L	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	166×10^4 / μ L	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	5.4×10^4 / μ L	Chloride	104 mEq/L
Reticulocyte count	2,000 / μ L	Calcium	8.1 mg/dL
Infection		Serum iron	240 μ g/dL
Parvovirus B19 PCR	<100 copy/mL	UIBC	13 μ g/dL
EBV		Ferritin	557.1 ng/mL
EA IgG	(+)	Vitamin B12	408 pg/mL
EBNA IgG	(+)	Folic acid	6 ng/mL
VCA IgG	(+)	Serology	
VCA IgM	(-)	CRP	0.3 mg/dL
Mumps		Rheumatoid factor	<10 IU/mL
IgM	(-)	Anti-nuclear antibody	20 Index
Neutralizing anti-body	(+)	Coagulation	
		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

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.

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/ μ L (0.1%), and unchanged thrombocytopenia secondary to splenomegaly and chronic liver dysfunction (Table 1). Iron, vitamin B12, and folic acid levels were normal. CT, esophagogastroduodenoscopy, and colonoscopy 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 infectiosum. The patient had no fever, exanthema, or arthralgia, and none of her family members had infections such as infectious mononucleo-

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 μ m.

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

Case No.	Reference No.	Age	Sex	Duration of exposure (months)	Days Recovery (Days)	Cooms 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	Type1 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	(-)
4	11	53	M	6	30	(-)	300	Pyr	(+)	6.9	0.1	Thalassemia
5	11	81	M	2	4	(-)	300	EB, Pyr	(+)	6.8	0.2	(-)
6	12	62	M	4	30-45	(-)	300	Pyr, PSL	(-)	9	0.2	COPD
7	12	72	M	6	60	NR	300	RFP, ASP	(+)	11.7	NR	Arrhythmia
8	9	77	M	3	14	NR	NR	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	NR	NR	NR	NR	(+)	4	0.3	(-)
16	This report	41	F	2.5	14	(-)	250	PSL	(+)	5.9	0.1	Sarcoidosis

PAS: para-amino salicylic acid, Pyr: Pyridoxine, EB: ethambutol, PB: Phenobarbitone, 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

sis or 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 viral 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.

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-

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
Cooms test	+ / -	2 / 7
Transfusion	Yes / No	13 / 3
Lowest Hb	g/dL	6.4
Lowest reticulocyte	%	0.2

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 (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.

In recent years, the increased use of biological preparations has increased the need for anti-tuberculous 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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