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【 CASE REPORT 】

Rhabdomyolysis Induced by Isoniazid in a Patient with Rheumatoid Arthritis and End-stage Renal Disease: A Case Report and Review of the Literature

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Abstract:
A 76-year-old man complicated with end-stage renal disease had latent tuberculosis infection (LTBI), and isoniazid (INH) 300 mg daily was started to prevent reactivation of LTBI before using biologic agents for rheumatoid arthritis. On the 8th day after administration of INH, he presented with a fever, petechiae, and myalgia. Serological studies revealed elevated myogenic enzymes and creatinine level. Based on the exclusion of other etiologies, rapid improvement with cessation of INH, and the recurrence of the fever and myalgia with re-administration of a reduced dose of INH, we diagnosed him with INH-induced rhabdomyolysis. Physicians should be aware of rhabdomyolysis induced by INH at a therapeutic dose as an infrequent but potentially fatal adverse drug reaction.

Key words: latent tuberculosis infection, rhabdomyolysis, isoniazid, rheumatoid arthritis, end-stage renal disease

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Introduction

Biologic agents have become a part of the mainstream therapy for rheumatoid arthritis (RA); however, the blockade of pro-inflammatory cytokines increases the risk of reactivation of intracellular pathogens, especially *Mycobacterium tuberculosis* (TB). To avoid the reactivation of latent TB infection (LTBI), appropriate screening and therapy for LTBI is necessary for patients with RA who plan to start biologic therapy (1).

Isoniazid (INH) is recommended for the standard treatment of LTBI (2) and is known to have a high efficacy for preventing the progression to active TB (3, 4). INH reduces active TB by approximately 85% in RA patients treated with biologic agents (1). INH is metabolized and cleared predominantly in the liver (5); well-known adverse drug reactions include neuropathy (6) and hepatotoxicity (7).

We herein report a rare case of rhabdomyolysis induced by INH at a therapeutic dose. Written informed consent for the publication was obtained from the patient.

Case Report

A 76-year-old Japanese man had a 17-year history of seropositive RA. He also had a history of chronic kidney disease (stage G5A3) with a glomerular filtration rate <15 mL/min due to nephrosclerosis. He had a history of treatment with methotrexate, sulfasalazopyridine, bucillamine, and tacrolimus, but the efficacy was limited. Subsequently, he was treated with prednisolone (5 mg daily) and lobenzarit (40 mg daily), but the disease activity remained high. Therefore, the use of biologic agents was considered. He had fibronodular changes in the upper lobes bilaterally and a positive tuberculin skin test. Therefore, LTBI was diagnosed. INH (300 mg daily) was started to prevent reactivation of LTBI before starting biologic agents.

On the 8th day after the administration of INH, he developed a fever, petechiae in the lower extremities, and intermittent myalgia in the thighs. A physical examination revealed tenderness in the thighs without muscle weakness. Serologic studies showed the following: creatine kinase,

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Table 1. Time Courses of Laboratory Findings.

	Baseline	8 Days after INH Intake	7 Days after INH Cessation	RV
WBC (10^3 cells/μL)	12.6	7.0	12.9	3.3 - 8.6
Neutrophil (%)	84.1	82.2	62.7	44 - 74
Lymphocyte (%)	9.1	10.4	28.0	30 - 40
Monocyte (%)	5.0	4.9	5.6	2 - 10
Eosinophil (%)	1.4	2.4	3.3	0 - 5
Basophil (%)	0.4	0.1	0.4	0 - 2
Hb (g/dL)	10.6	9.4	9.0	13.7 - 16.8
Platelet (10^4 cells/μL)	23.6	14.9	37.0	15.8 - 34.8
Procalcitonin (ng/mL)	not evaluated	2.49	not evaluated	0 - 0.49
CK (U/L)	70	11,253	23	59 - 248
CK-MB (U/L)	not evaluated	13	7	0 - 12
BUN (mg/dL)	36.5	43.0	36.5	8.0 - 20.0
Cr (mg/dL)	2.30	3.80	2.40	0.65 - 1.07
AST (U/L)	15	182	19	13 - 30
ALT (U/L)	9	14	32	10 - 42
CRP (mg/dL)	0.28	13.72	0.86	0.0 - 0.3

INH: isoniazid, RV: reference value, WBC: white blood cell, Hb: hemoglobin, CK: creatine kinase, BUN: blood urea nitrogen, Cr: creatinine, Mb: myoglobin, AST: aspartate transaminase, ALT: alanine transaminase, CRP: C-reactive protein

11,253 U/L [reference value (RV), 59-248 U/L]; myoglobin, 13,900 ng/mL (RV, <154.9 ng/mL); and creatinine, 3.8 mg/dL (RV, 0.65-1.07 mg/dL; Table 1). The urine myoglobin level was also elevated to 21,850 ng/mL (RV, <10 ng/mL). Based on a detailed medical interview, prior trauma, muscle compression, heat stroke, and infection were excluded. All bacterial cultures were negative, and viral antibody tests excluded a viral infection. Thyroid function tests were within normal limits, and autoantibodies against Jo-1 and aminoacyl tRNA synthetase were not detected. All drugs, except for INH, had been taken for a long period of time, and statins were not included. The serum concentrations of INH at 3 and 24 hours after the last INH administration were 2.93 and 0.58 μg/mL, respectively, which was consistent with a previous pharmacokinetic study (8). The cessation of INH and intravenous hydration significantly ameliorated the rhabdomyolysis and acute kidney injury within 7 days (Table 1). The re-administration of INH at a reduced dose to 200 mg every other day was planned 1 month after his complete recovery of rhabdomyolysis under hospitalization with detailed informed consent. He developed a fever and systemic myalgia with a single-dose administration of 200 mg INH, although his serum creatine kinase (CK) level was not elevated.

Discussion

Rhabdomyolysis is a life-threating condition resulting from the breakdown of muscles and leakage of muscle cell contents (9). Medications are a potential cause of this condition, and lipid-modifying agents, including hydroxymethylglutaryl (HMG)-CoA reductase inhibitors, antipsychotics, and anesthetic agents, are frequently reported to the US Food and Drug Administration (FDA) as causes of drug-associated rhabdomyopathy (10). Although rhabdomyolysis induced by an overdose of more than 2.4 g INH has been reported (11-13), there are quite a few case reports of rhabdomyolysis induced by INH at therapeutic doses (14, 15) (Table 2). Our case differs from these reports in that rhabdomyolysis occurred only several days after the INH intake, but the clinical course implied that INH induced rhabdomyolysis as an adverse drug reaction based on the two causality assessment systems proposed by Naranjo (16) (Table 3) and the World Health Organization Uppsala Monitoring Centre (WHO-UMC) (17) (Table 4). Dose adjustment of INH for renal impairment is usually unnecessary because INH is metabolized and cleared predominantly in the liver, and our patient did not have a significant elevation in the serum concentration of INH. However, decreased isoniazid acetylation in chronic renal failure (18) can cause the accumulation of hydrazine, a metabolite of INH, as the concentration of hydrazine is predicted to be high in slow acetylators (19). Further pharmacokinetic analyses of INH and its metabolites in end-stage renal failure are awaited.

Our patient's rapid development of recurrent adverse events on the re-administration of INH suggests an allergic mechanism. However, in contrast to the previous reports of rhabdomyolysis and hypersensitivity syndrome (20-25), our case did not present with typical skin rashes or a fever and myalgia, suggesting that other etiologies may have induced the adverse events.

One of the mechanisms suspected to underlie rhabdomyolysis is the depletion of ATP within myocytes (9). Recently, statin-induced myopathy has been reported to be caused by the inhibition of mitochondrial respiration and ATP production (26). In addition, INH induces mitochon-

Table 2. Literature Review of Isoniazid-induced Rhabdomyolysis.

Case	Age	Sex	Ethnicity	Application of INH	Dosage of INH	Comorbidities and risks	Maximal CK levels	Reference No.
1	17	F	n.d.	Positive PPD test	10.8 g (intoxication)	Seizure, Hepatitis	88,000 U/L (RV<390)	12
2	16	M	n.d.	Tuberculosis prophylaxis	6.0 g (intoxication)	Seizure, Usage of intramuscular pyridoxine	22,673 U/L (RV; n.d.)	13
3	25	F	Blacks	Positive PPD test	300 mg daily for 4 months (poor compliance)	Preceding viral infection	168,000 U/L (RV; n.d.)	14
4	56	M	Chinese	Treatment of pulmonary TB	300 mg daily for 5 months	Dilated cardiomyopathy Chronic heart failure	14,781 U/L (RV<306)	15
5	76	M	Japanese	Prevention for LTBI	300 mg daily for 8 days	Rheumatoid arthritis End-stage renal disease	11,253 U/L (RV<248)	Present case

INH: isoniazid, TB: tuberculosis, LTBI: latent TB infection, CK: creatine kinase, RV: reference value, PPD: purified protein derivative, n.d.: not demonstrated

Table 3. Systematic Causality Assessment by Naranjo's Algorithm.

Questionnaire	Score	Score of Our Case
1. Are there previous conclusive reports on this reaction?	YES=+1 NO=0 Do not know or not done=0	0
2. Did the adverse event appear after the suspected drug was administered?	YES=+2 NO=-1 Do not know or not done=0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	YES=+1 NO=0 Do not know or not done=0	+1
4. Did the adverse reaction reappear after the drug was readministered?	YES=+2 NO=-1 Do not know or not done=0	+2
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	YES=-1 NO=+2 Do not know or not done=0	+2
6. Did the reaction reappear when a placebo was given?	YES=-1 NO=+1 Do not know or not done=0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	YES=+1 NO=0 Do not know or not done=0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	YES=+1 NO=0 Do not know or not done=0	+1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	YES=+1 NO=0 Do not know or not done=0	0
10. Was the adverse event confirmed by any objective evidence?	YES=+1 NO=0 Do not know or not done=0	+1
Scoring: >8=definite ADR, 5-8=probable ADR 1-4=possible ADR, 0=Doubtful ADR		Total score: 9

ADR: adverse drug reaction

drial dysfunction and ATP depletion, which results in hepatocellular injury (27). INH can inhibit the mitochondrial function and cause rhabdomyolysis via a mechanism similar to that of statin-induced rhabdomyolysis. Our case indicates that INH at a therapeutic dose can induce rhabdomyolysis, and caution should therefore be practiced when prescribing INH.

Author's disclosure of potential Conflicts of Interest (COI).
Toshihiko Komai: Patent royalties, Chugai Pharmaceutical. Shuji Sumitomo: Honoraria, AbbVie, Eisai, Chugai Pharmaceutical, Takeda, Bristol-Myers Squibb, Astrazeneca and UCB. Keishi Fu-

Table 4. Systematic Causality Assessment by World Health Organization Uppsala Monitoring Centre.

Assessment Criteria of Causality 'Probable/Likely'	Our Case
· Event of laboratory test abnormality, with reasonable time relationship to drug intake	Yes
· Unlikely to be attributed to disease or other drugs	Yes
· Response to withdrawal clinically reasonable	Yes
· Rechallenge not required	

jio: Patent royalties, Chugai Pharmaceutical; Honoraria, Bristol-Myers Squibb, Chugai Pharmaceutical, Pfizer, AbbVie, Eli Lilly, Astellas Pharma, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Santen, Takeda, Eisai, Taisho Toyama, UCB, Janssen and Nippon Kayaku; Research funding, Takeda Pharmaceutical, Chugai Pharmaceutical, Bristol-Myers Squibb, Mitsubishi Tanabe Pharma, Eli Lilly and Astellas Pharma.

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