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

Toshihiko Komai, Shuji Sumitomo, Shuzo Teruya and Keishi Fujio

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

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,
Table 1. Time course of laboratory findings.

|                      | Baseline | 8 days after INH intake | 7 days after INH cessation | RV       |
|----------------------|----------|-------------------------|---------------------------|----------|
| WBC (10^3 cells/mL)  | 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 (10^3 cells/mL) | 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

Discussion

Rhabdomyolysis is a life-threatening 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 se-
rum 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 mitoc

### Table 2. Literature Review of Isoniazid-associated 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 <90) | 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 cardiomypathy 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, CK: creatine kinase, RV: reference value, 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 | 0                 |
| NO = 0                                                                        |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 2. Did the adverse event appear after the suspected drug was administered?   | YES = +2 | +2                |
| NO = -1                                                                       |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | YES = +1 | +1                |
| NO = 0                                                                        |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 4. Did the adverse reaction reappear after the drug was readministered?      | YES = +2 | +2                |
| NO = -1                                                                       |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? | YES = -1 | +2                |
| NO = +2                                                                       |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 6. Did the reaction reappear when a placebo was given?                       | YES = -1 | 0                 |
| NO = +1                                                                       |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | YES = +1 | 0                 |
| NO = 0                                                                        |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | YES = +1 | +1                |
| NO = 0                                                                        |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | YES = +1 | 0                 |
| NO = 0                                                                        |       |                   |
| Do not know or not done = 0                                                   |       |                   |
| 10. Was the adverse event confirmed by any objective evidence?                | YES = +1 | +1                |
| NO = 0                                                                        |       |                   |
| Do not know or not done = 0                                                   |       |                   |

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.

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 | |

References

1. Winthrop KL, Chiller T. Preventing and treating biologic-associated opportunistic infections. Nat Rev Rheumatol 5: 405-410, 2009.
2. McClintock AH, Eastment M, McKinney CM, et al. Treatment completion for latent tuberculosis infection: a retrospective cohort study comparing 9 months of isoniazid, 4 months of rifampin and 3 months of isoniazid and rifapentine. BMC Infect Dis 17: 146, 2017.
3. (No authors listed.). Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med 161: S221-S247, 2000.
4. Stagg HR, Zener D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of Latent Tuberculosis Infection. Ann Intern Med 161: 419, 2014.
5. Wang P, Pradhan K, Zhong X, Ma X. Isoniazid metabolism and hepatotoxicity. Acta Pharm Sin B 6: 384-392, 2016.
6. Vilholm OJ, Christensen AA, Zedan AH, Itani M. Drug-Induced Peripheral Neuropathy. Basic Clin Pharmacol Toxicol 115: 185-192, 2014.
7. Nolan CM, Goldberg S V, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA 281: 1014-1018, 1999.
8. Peloquin CA, Jaresko GS, Yong CL, Keung ACF, Bulpitt AE, Jelliffe RW. Population pharmacokinetic modeling of isoniazid, rifampin, and pyrazinamide. Antimicrob Agents Chemother 41: 2670-2679, 1997.
9. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med 361: 62-72, 2009.
10. Oshima Y. Characteristics of drug-associated rhabdomyolysis: analysis of 8,610 cases reported to the U.S. Food and Drug Administration. Intern Med 50: 845-853, 2011.
11. Panganiban LR, Makalinao IR, Corte-Maramba NP. Rhabdomyolysis in isoniazid poisoned. J Toxicol Clin Toxicol 39: 139-151, 2001.
12. Blower DL, Johnson D, Verjee Z. Isoniazid-associated rhabdomyolysis. Am J Emerg Med 13: 543-548, 1995.
13. Eyüboğlu T, Derinöz O. Rhabdomyolysis due to isoniazid poisoning resulting from the use of intramuscular pyridoxine. Turk J Pediatr 55: 328-330, 2013.
14. Cronkright PJ, Szyniaki G. Isoniazid and rhabdomyolysis. Ann Intern Med 110: 945, 1989.
15. Liu P, Zheng H, Yuan W, Nie R, Wang J. Isoniazid-induced rhabdomyolysis in a patient with chronic heart failure: a case report. Chin Med J (Engl) 123: 502-504, 2010.
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30: 239-245, 1981.
17. Varallo FR, Planeta CS, Herdeiro MT, Mastroianni P, de C. Implication of adverse drug reactions: Causality assessment in hospitals. Oiso N, editor. PLoS One 12: e0171470, 2017.
18. Kim YG, Shin JG, Shin SG, Jang JH, Kim S, Lee JS, et al. Decreased acetylation of isoniazid in chronic renal failure. Clin Pharmacol Ther 54: 612-620, 1993.
19. Federico F, Rosanna M, Missimo B, Giovanni T, Mario F. Isoniazid and its Hydrazine Metabolite in Patients with Tuberculosis. Clin Drug Invest 17: 145-154, 1999.
20. Arnold PA, Guglielmo BJ, Holland H. Severe hypersensitivity reaction upon rechallenge with trimethoprim-sulfamethoxazole in a patient with AIDS. Drug Intell Clin Pharm 22: 43-45, 1988.
21. Compton MR, Crosby DL. Rhabdomyolysis associated with azathioprine hypersensitivity syndrome. Arch Dermatol 132: 1254-1255, 1996.
22. Rahman Z, Weinberg J, Scheinfeld N. Minocycline hypersensitivity syndrome manifesting with rhabdomyolysis. Int J Dermatol 41: 530-531, 2002.
23. Kong Q, Sang H, Zhang M, Zeng M, Hu WX, Deng DQ, et al. Rhabdomyolysis associated with roxithromycin hypersensitivity syndrome. Indian J Dermatol Venereol Leprol 78: 197-199, 2012.
24. Huang LY, Lin CM, Chiu CC, Lin WS, Cheng SM. Rhabdomyolysis as a potential complication of carbamazepine-induced toxic epidermal necrolysis. Clin Biochem 45: 1531-1532, 2012.
25. Kellett S, Cock C. A case of drug reaction with eosinophilia and
systemic symptoms. Case Rep Med 2012; 705190, 2012.

26. Schirris TJJ, Renkema GH, Ritschel T, et al. Statin-induced myopathy is associated with mitochondrial complex III inhibition. Cell Metab 22: 399-407, 2015.

27. Lee KK, Fujimoto K, Zhang C, et al. Isoniazid-induced cell death is precipitated by underlying mitochondrial complex I dysfunction in mouse hepatocytes. Free Radic Biol Med 65: 584-594, 2013.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).