HLA-B 15:13 Positive in an Indonesian Patient with Phenytoin-Induced SJS/TEN

by Putu Devi Oktapiani Putri1

Submission date: 04-Jul-2023 09:58PM (UTC+0800)
Submission ID: 2126431535
File name: HLA-B_15_13_Positive_in_an.pdf (308.23K)
Word count: 2170
Character count: 11833

CASE REPORT

HLA-B 15:13 Positive in an Indonesian Patient with Phenytoin-Induced SJS/TEN

Putu Devi Oktapiani Putri[1], Afif Nurul Hidayati[2], Betty Agustina Tambunan[3], Andrea Hertanto[4]

[1] Clinical Pathology Specialization Program, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, 60286 Surabaya, Indonesia
[2] Department of Dermatology and Venerology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, 60286 Surabaya, Indonesia
[3] Immunology Division, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, 60286 Surabaya, Indonesia
[4] Dermatology and Venerology Specialization Program, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, 60286 Surabaya, Indonesia

ABSTRACT

Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe forms of delayed hypersensitivity reaction with an underlying immunologic mechanism involving the interaction between HLA and drug molecules. A-35-year-old Javanese-Indonesian-male, with a history of seizures, presented with skin peeling, mucosal erosions, and purulent eye discharges. He was clinically diagnosed as overlapping SJS/TEN, and both phenytoin and valproic acid became the suspected drugs. Unfortunately, the seizure relapsed and alternative antiepileptic drugs were urgently needed. HLA typing was then performed, revealing the presence of HLA-B*15:13, which has been proven to be correlated with phenytoin adverse reaction by previous study. Thus, phenytoin was totally discontinued and he only prescribed monotherapy valproic acid. Given the high prevalence and common use of phenytoin in clinical practice, HLA evaluation before phenytoin prescription in Indonesia is important. Further studies are recommended to provide more evidence regarding the role of HLA-B*15:13 in phenytoin-induced severe hypersensitivity reactions in Indonesia.
Malaysian Journal of Medicine and Health Sciences (2023) 19(1):369-371. doi:10.47836/mjmhs19.1.47

Keywords: Steven-Johnson Syndrome, Phenytoin, HLA

Corresponding Author:
Betty Agustina Tambunan, Sp.PK(K)
Email: betty-a-t@fk.unair.ac.id
Tel: +6231-5501078

INTRODUCTION

Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare, life-threatening disorders characterized by severe skin and mucous membrane manifestations, with a high mortality rate. The spectrum of SJS ranges from SJS, SJS/TEN overlap, and TEN with the involvement of skin detachment <10%, 10-30%, and >30%, respectively (1). Recently, HLA-B*15:13 has been associated with phenytoin-induced severe cutaneous adverse drug reaction in Malaysia, with an eight-fold risk of having SJS/TEN compared to tolerant control (2). The allele frequency of HLA-B*15:13 among the Javanese population in Indonesia is high, ranging from 12.5% (3) to 21.6% (4). Here we present a case of an Indonesian male with HLA-B*15:13 positive who developed SJS/TEN after consumption of phenytoin.

CASE REPORT

A-35-year-old Javanese-Indonesian-male has a history of focal to generalized tonic-clonic seizures. He had a motorcycle accident 4 years earlier, and a head surgery had to be performed thereafter. Head CT scan revealed the presentation of right temporal lobes gliosis of cortex-subcortex parenchyma, moreover, the EEG result showed a sharp wave with continuous slow activity at the right temporal region which potentially epileptogenic. Monotherapy of valproic acid 3 x 250 mg was prescribed as the first medication. However, it caused the seizures to recur up to 6 times a year. Therefore, the neurologist prescribed phenytoin 3 x 100 mg in addition to valproic acid 3 x 250 mg. There was no relapse after the combination of those medications. Unfortunately, 45 days later, he experienced fever and malaise followed by skin rash. The skin lesion manifested as erythematous skin over the neck and spread throughout the chest, back, and arm. Bullae appeared the next day followed by peeling of the skin. Jaundice manifested after five days. At the time of

presentation in the emergency room, the bullae had been resolved. He presented with skin detachment mainly over the chest, peeling skin on the glans penis, erosion with haemorrhagic crusts on the lips (Fig. 1), purulent discharge from both eyes, and jaundice. He has no previous history of allergy.

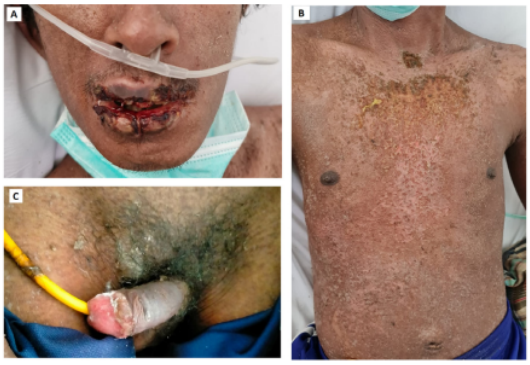

Figure 1: Clinical presentations of the patient at admission time (7 days after the onset) Erosion with haemorrhagic crust on lips (A) Skin detachment with pus on chest and abdomen (B) Skin detachment on the glans penis (C)

This patient was presented with involvement of 13% body surface area and diagnosed as SJS/TEN overlap by the dermatologist. He received oxygen supplementation, intravenous fluid therapy, followed by intravenous dexamethasone injection, and topical skin antibiotic. He was also referred to the ophthalmologist and received antibiotic eye drops. The intravenous steroid therapy was administered for seven days, followed by 30 days oral methylprednisolone for tapering of the dosage. The detail of the laboratory result is shown in Table I. Hepatitis B Surface Antigen (HBsAg) and anti-HCV antibody showed negative results. The eosinophil count was $0.01x10^3$ cells/µL on the first day of admission with a maximum count of 0.3×10^3 cells/µL within the period of hospitalization.

After three days of hospitalization, he started to have a cough, shortness of breath, and fever. Paracetamol was administered to relieve the fever. Leukocyte count increased to 28.46×10^3 /µL with neutrophil predominant, and sputum culture revealed the infection of *Pseudomonas aeruginosa*. Levofloxacin 750 mg was given intravenously for seven days. There was no new skin lesion observed within 24-hour of follow-up. The clinical picture and laboratory parameters were improved. The level of ALT, AST, DBIL, and TBIL decreased gradually, reaching the expected level at the end of follow-up. He was discharged after nine days of hospitalization.

Phenytoin and valproic acid were suspected of becoming the associated drugs; thus, the algorithm for causality of epidermal necrolysis ALDEN score was calculated and resulted in a very probable score for phenytoin and very unlikely for valproic acid (Table II). Both drugs were discontinued to avoid further harmful reactions. The confirmatory test was planned to be performed six weeks after the discontinuation of oral methylprednisolone. Unfortunately, the seizure relapsed within the period of waiting for the test, and the neurologist could not prescribe the same medications.

Table I: Laboratory Results

Parameters	7th day*	10th day*	13th day*	27th day*	36th day*	Reference range
ALT (U/L)	251	137	134	77	46	16 – 63
AST (U/L)	63	60	49	45	22	15 – 37
DBIL (mg/dL)	5.99	3.29	2.24	0.87	0.38	<0.3
TBIL (mg/dL)	7.92	4.22	2.58	1.54	0.60	0.2 – 1.0
ALP (U/L)	414					46 – 116
GGT (U/L)	653.7					15 – 85

*Days following disease onset
Laboratory results from the day of admission (7th day following disease onset) show liver involvement with mixed hepatocellular and cholestatic patterns (increased transaminase enzyme, bilirubin, ALP, and GGT). He was discharged on the 13th day following the onset and visited as an outpatient on the 27th and 36th days following disease onset. ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Transaminase; GGT: Gamma Glutamyl Transferase

Table II: The ALDEN Score Calculation

Criteria	Phenytoin	Valproic Acid
Delay from initial drug component intake to onset of reaction (index day)	2	2
Drug present in the body on index day	0	0
Pre-challenge/rechallenge	1	-2
De-challenge	0	0
Type of drug (notoriety)	3	-1
Other cause	0	0
Final score –12 to 10	6	-1

Interpretation <0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable

HLA typing was then performed by collecting blood specimens and harvesting the peripheral blood mononuclear cells. We used sequence-specific oligonucleotide-primed PCR (PCR-SSO) by Luminex® Technology to obtain all the possible allele codes, and the result is shown in Table III. Considering the history of SJS/TEN, all the suspected drugs, and the result of the HLA typing evaluation, this patient was given only valproic acid, and phenytoin was totally discontinued. Monitoring for the potential hypersensitivity reaction was done, and there was no such reaction found until seven days after valproic acid consumption. Finally, with very careful observations, a challenge test was performed six weeks after the last steroid consumption. One hour after administering 100 mg oral phenytoin, itchy-erythematous skin started to spread from his upper leg onto the neck. Steroid and antihistamine were immediately administered, and phenytoin was discontinued.

DISCUSSION

Finding the causality is crucial in severe hypersensitivity reactions. In this case, this patient needs continuous

Table III: The Result of HLA-B Genotyping

HLA Typing	Possible Allele Codes
B*15:13 B*35:01	B*15:XX1 and B*35:XX2 XX1:=:15:13/15:418 XX2:=:35:01/35:07/35:30/35:40N/35:41/35:42/35:53N/35:77

The result of HLA-B genotyping shows all possible allele codes carried by this patient. HLA genotyping was performed using PCR SSO method by Luminex®.

long-term use of medication for epilepsy. Although the ALDEN score calculation (1) resulted in phenytoin as a probable cause (Table II), it should be emphasized that other possibilities could not be ruled out. The drug challenge test may reveal the causative drugs, but the potentially harmful reactions can become a concern. Considering the severe hypersensitivity reaction of this patient, in vitro diagnostic test is preferable. Alternatively, skin prick or patch tests may be beneficial; however, they should be performed after the discontinuation of steroids and the total disappearance of the skin lesion. Meanwhile, there is an urgent need to find the causative drug and decide the alternative drugs for this patient. Evaluation of HLA in this patient finally can support the decision-making.

The frequency of HLA-B*15:13 in the West Java population of Indonesia is about 21,6% (4). It also has been studied that HLA-B*15:13 is associated with phenytoin-induced SJS in the Malaysian population. Patient with one copy risk of allele (HLA-B*15:02 or HLA-B*15:13) has 8,62 times the risk of developing SJS; moreover, it has become 57,5% if two copies of the allele are present (2). Information regarding the positive result of HLA-B*15:13 can potentially prevent unnecessary exposure of the patient to phenytoin. Furthermore, the result of HLA typing could be established within 24 – 48 hours, it also can be performed within the period of the disease, and there is no need to wait until the discontinuation of corticosteroids.

Screening for HLA genotype before drug prescription should be considered due to the highly used phenytoin as an anticonvulsant in Indonesia (5). Unfortunately, there is still a lack of evidence regarding the correlation between HLA-B*15:13 and phenytoin-induced adverse drug reaction (ADR) in Indonesia. Increasing the number of evidence for specific HLA types related to ADR will be beneficial because it will influence the decision-making in clinical practice. However, further studies about the correlation between HLA-B*15:13 with SJS or other ADR and its cost-effectiveness in Indonesia are required.

CONCLUSION

HLA-B*15:13 can increase the risk of SJS/TEN in phenytoin use. Genetic screening before prescribing high-risk medication is essential to avoid potential harmful hypersensitivity reactions. Further studies in Indonesia are needed to determine the significance of HLA-B*15:13 in severe hypersensitivity reactions, particularly when phenytoin is used.

ACKNOWLEDGEMENTS

The authors would like to thank Department of Clinical Pathology and Department of Dermatology and Venerology of Dr. Soetomo Hospital for the availability of patient's information. This report has been approved by The Ethical Committee of Dr. Soetomo Hospital Surabaya, and written consent has been obtained from the patient.

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