High-Dose Vitamin D3 and Tonsillectomy as Therapeutic Management in Henoch–Schönlein Purpura Following Hepatitis B Vaccination: A Rare Case Report

Agus Joko Susanto[1,2], Felizia Alika Yusman[2], Fatna Andika Wati[1,2], Yeremia Suryo Pratama[2]*

[1]Division of Clinical Allergy and Immunology, Department of Internal Medicine, Dr. Moewardi Hospital, Surakarta, Indonesia.
[2]Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia.

**** Corresponding Author:***
Agus Joko Susanto, MD. Department of Internal Medicine, Faculty of Medicine, Sebelas Maret University. Jl. Kolonel Soetarto no. 132, Jebres, Surakarta 57126, Indonesia. E-mail address: agusjoko.susanto4@gmail.com.

ABSTRACT

Henoch–Schönlein purpura (HSP) is an immunoglobulin A (IgA)-mediated systemic vasculitis, which is one of the rare adverse reactions to hepatitis B vaccination. Low vitamin D levels were found to be present in the majority of HSP patients.

A 19-year-old woman was admitted with a purpuric rash on bilateral lower limbs and joint pain on her left index finger in January 2020. A previous history of rash occurred one week after the patient received her first dose of recombinant hepatitis-B vaccination. Routine hematological examination, creatinine, urinalysis, C3, and C4 showed normal results. HBsAg, Anti-HCV, and ANA tests were negative, and anti-HBs were elevated. Vitamin D is very low. The patient was diagnosed with HSP and given mycophenolate mofetil, methylprednisolone, vitamin D3, and folic acid. Within 1 month of therapy, the rash still occurred frequently, so mycophenolate mofetil was changed to mycophenolic acid, the dose of methylprednisolone was increased and fexofenadine was administered. In the next 3 months, the rash has improved. However, patients reported knee joint pain and hair loss. In May 2021, the patient underwent tonsillectomy due to acute exacerbation of chronic tonsillitis. Thereafter, the patient reported that the rash had completely resolved and never worsened, and the vitamin D assay was normal.

Hepatitis B vaccination is one of the etiologies of HSP, although it is rare, so it is important to ask about the vaccination history in patients with suspected HSP. Correction of vitamin D and performing tonsillectomy provide better treatment results in HSP cases in this patient.

***Keywords**: Vitamin D3, tonsillectomy, Henoch–Schönlein purpura, hepatitis B vaccination.*

INTRODUCTION

Henoch–Schönlein purpura (HSP) is an immunoglobulin A (IgA)-mediated systemic vasculitis defined by the clinical triad of nonthrombocytopenic palpable purpura, abdominal discomfort, and arthritis.[1] This is the most prevalent form of systemic vasculitis in children, with an incidence rate of between 6 and 22 per 100,000 person-years Clicktaps. This vasculitis was more uncommon in adults, with an incidence rate between 3.4 and 14.3 per 100,000 person–years.[1] The incidence of this vasculitis does not differ between genders; however, the recurrence rate is nearly twice as high in males.[2] HSP is a rare complication of infectious diseases, and a significant percentage of HSP patients have

a recent history of upper respiratory infection. More rare predisposing factors include exposure to insect bites, immunizations, medications, or dietary allergies.[3]

Vitamin D exhibits a range of immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant properties in addition to its calcium homeostasis regulator activities.[4,5] Vitamin D or 1,25 dihydroxy vitamin D has immune regulatory effects on innate and adaptive immune responses,[6] and low vitamin D may decrease self-tolerance in genetically susceptible individuals by impairing the control of dendritic cells, regulatory T-lymphocytes, and Th1 cells.[7] Several autoimmune disorders were associated with low vitamin D levels, such as multiple sclerosis, systemic scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and rheumatic heart disease.[6] In several studies, low vitamin D levels were found to be present in the majority of HSP patients.[8,9]

Type B viral hepatitis is a severe and potentially fatal disease that is easily prevented by vaccination. Hepatitis B vaccines are extraordinarily safe, and infrequently mild and transient adverse reactions to hepatitis B vaccination are observed.[10] Vasculitis, including HSP,[11] is one of the rare adverse reactions, and it has been scarcely reported in the past decade.[12–14] There were only 8 cases of cutaneous vasculitis previously reported, namely 4 cases of cryoglobulinemia detected with 1 patient type II (mixed) and 1 case of transient proteinuria.[15] The purpose of this case report was to describe the first case of HSP in a 19-year-old Indonesian woman following hepatitis B vaccination, which was successfully treated with a high dose of vitamin D3 and tonsillectomy.

CASE ILLUSTRATION

In January 2020, a 19-year-old Indonesian woman was admitted to an outpatient care unit with a sudden purpuric rash on her bilateral lower legs (**Figure 1A**) and joint pain on her left index finger. The rash was palpable, painful, and not itchy. This was the second time the rash appeared in the lower extremities; the first one occurred 1 week after the first dose of recombinant hepatitis B (Euvax B) vaccination 3 months prior accompanied by acute abdominal pain and fresh bloody stool. The previous rash was treated with a symptomatic regimen, including topical and oral steroids, and resolved. Her medical history included multiple allergies and chronic tonsillitis that have been treated conservatively by an otorhinolaryngologist.

Routine hematological, glucose, HbA1c, lipid profile, creatinine, uric acid, and urinalysis were performed and showed unremarkable results. Antistreptolysin O titer, anti-human

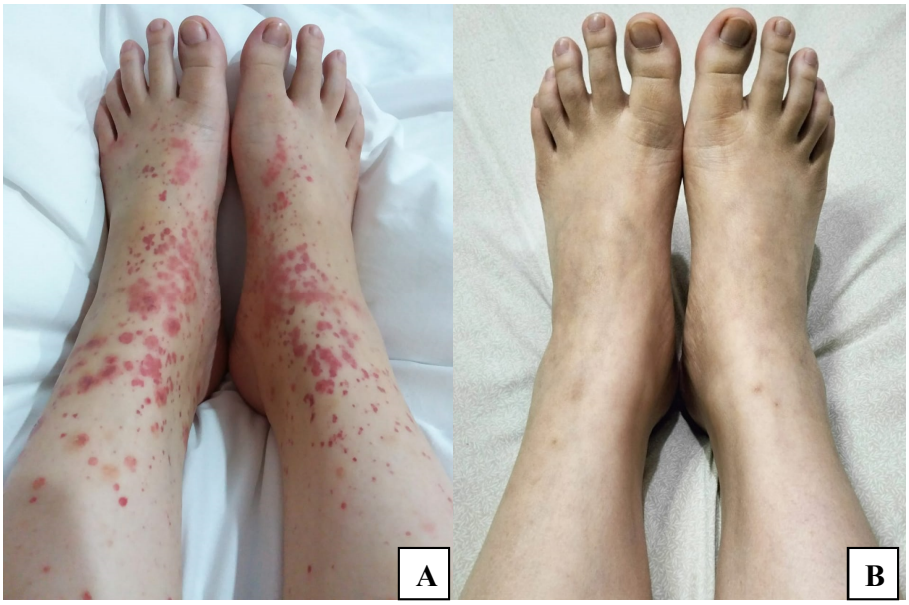

Figure 1. Clinical picture of the bilateral purpuric palpable rash of the patient. A, on presentation; B, bilateral rash resolution following 19 months of follow up period.

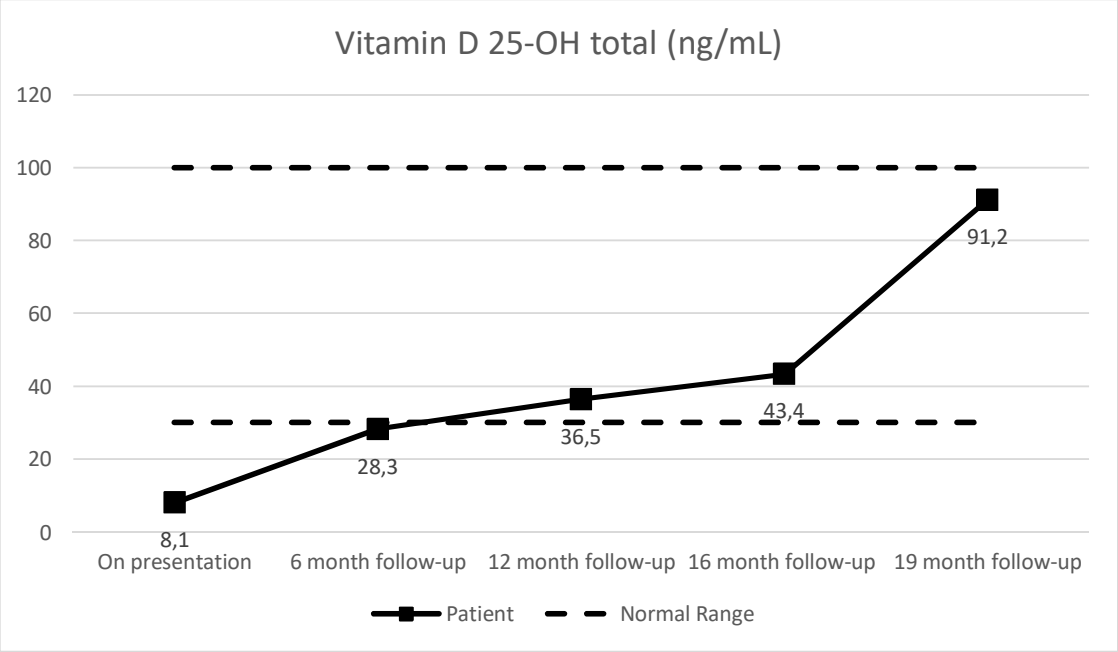

Figure 2. Vitamin D examination of the patient from presentation to the last follow-up visit. The vitamin D continued to increase gradually. It reached the normal range on the 12-month follow-up and continued to increase on the 19-month follow-up.

immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and anti-hepatitis C virus (HCV) showed negative results, and anti-HBs were elevated. C3 and C4 were in the normal range, but the vitamin D was remarkably low (8.1 ng/mL). ANA IF and profile test showed negative results, but the serum IgE panel test confirmed the multiple allergies in the patient (**Table 1**).

HSP then was established based on clinical criteria (**Table 2**), and the patient was given mycophenolate mofetil 500 mg/day, methylprednisolone 8 mg/day, vitamin D3 1000 IU b.i.d., and folic acid 400 µg/day.

During the 1-month follow-up, the patient reported frequent exacerbations of the rash, and the drug regimen was changed to as follows: fexofenadine 120 mg/day, mycophenolic acid

Table 1. Results of laboratory and immunology investigations in the patient at presentation

Parameter	Value
Hemoglobin (g/dL)	13.2
Platelets (10^3/µL)	333
WBC (10^3/µL)	7.5
Creatinin (mg/dL)	0.55
Fasting glucose (mg/dL)	76
HbA1C (%)	4.6
Cholesterol LDL (mg/dL)	161
Triglycerides (mg/dL)	60
Uric acid (mg/dL)	5.3
Urinalysis	
Color	Light yellow
Appearance	Clear
pH	7.0
Specific gravity	1.004
Leukocyte esterase	–
Nitrit	–
Albumin	–
Glucose	–
Keton	–
Urobilinogen	–
Bilirubin	–
Blood	–
Casts	–
Cell/epithelium	–
Bacteria	–
Crystal	–
Antistreptolysin O	<200
Anti-HIV	Nonreactive
HBsAg	Nonreactive
Anti-HCV	Nonreactive
Anti-HBs (mIU/mL)	94.42
C3 (mg/dL)	96.8
C4 (mg/dL)	19.9
Vitamin D 25-OH total (ng/mL)	8.1
ANA IF	Negative
ANA profile	Negative
Serum IgE panel	
Tyrophagus putrescentiae	++
Cockroach	+++++
Shellfish	++++

Table 2. Diagnostic criteria for HSP as developed by EULAR/PRINTO/PRES

Criteria	Description
Mandatory criteria	Purpura or petechiae with lower limb predominance
Minimum 1 out of 4 criteria	Diffuse abdominal pain with acute onset
	Histopathology showing leukocytoclastic vasculitis or proliferative glomerulonephritis, with predominant IgA deposits
	Arthritis or arthralgia of acute onset
	Renal involvement in the form of proteinuria or hematuria

EULAR/PRINTO/PRES: the European League Against Rheumatism, the Paediatric Rheumatology International Trials Organization, and the Paediatric Rheumatology European Society[20]

180 mg b.i.d., and methylprednisolone 8 mg b.i.d. Vitamin D3 and folic acid supplementation remained the same.

Observations over the next 3 months revealed that the rash became infrequently exacerbated, leaving hyperpigmented and unpalpable patches. However, the patient reported moderate knee joint pain and moderate hair loss. The diagnosis of osteoarthritis of the knee and telogen effluvium was considered, and the patient was referred to a medical rehabilitation department and dermatologist. The rehabilitation program included cryotherapy and a routine stationary cycling program. A combination of minoxidil 5% and mometasone furoate 0.1% was prescribed by the dermatologist for topical scalp application. The dose of methylprednisolone was then reduced to 4 mg/day.

The complication was resolved, and the rash was also rarely exacerbated in 2 months of follow-up. Additional laboratory assessment showed low vitamin D (28.3 ng/mL) and normal renal function. The drug regimen was adjusted to mycophenolic acid 180 mg at the one-day interval, and methylprednisolone 4 mg two times a week. Then, the patient was scheduled for monthly monitoring. Another vitamin D laboratory finding in December 2020 showed a normal result (36.5 ng/mL).

In May 2021, the rash was still persistent, albeit rarely exacerbated, and her vitamin D showed a normal result (43.4 ng/mL). This improvement in vitamin D was deemed unremarkable; thus, the vitamin D dose was adjusted to 15.000 IU/day paired with 90 mcg of vitamin K2/day for the next 3 months. Concurrently, the patient had an episode of acute exacerbation of chronic tonsillitis. The patient was then referred to an otorhinolaryngologist, and a tonsillectomy was performed. At the next follow-up, the patient reported that the rash was completely resolved and never exacerbated, and the vitamin D examination showed a normal result (91.2 ng/mL).

DISCUSSION

A 19-year-old woman was admitted with a purpuric rash on bilateral lower limbs and joint pain on her left index finger in January 2020. A previous history of rash occurred one week after the patient received her first dose of recombinant hepatitis-B vaccination. Routine hematological examination, creatinine, urinalysis, C3, and C4 showed normal results. HBsAg, Anti-HCV, and ANA tests were negative, and anti-HBs were elevated. Vitamin D is very low. The patient was diagnosed with HSP and given mycophenolate mofetil, methylprednisolone, vitamin D3, and folic acid. Within 1 month of therapy, the rash still occurred frequently, so mycophenolate mofetil was changed to mycophenolic acid, the dose of methylprednisolone was increased and fexofenadine was administered. In the next 3 months, the rash has improved. However, patients reported knee joint pain and hair loss. In May 2021, the patient underwent tonsillectomy due to acute exacerbation of chronic tonsillitis. Thereafter, the patient reported that the rash had completely resolved and never worsened, and the vitamin D assay was normal.

Immunization against hepatitis B is crucial as hepatitis B virus (HBV) role in liver carcinoma and is a substantial source of morbidity and death globally. Currently, the vaccine for hepatitis B contains recombinant HBsAg protein (5–40 μg) and adjuvants such as aluminum phosphate or aluminum hydroxide. Primary doses are administered twice a month apart, with the third dose as a booster 6 months later. The vaccine is injected intramuscularly at the anterior thigh or deltoid muscle.[10] In this case, the patient's left deltoid muscle was injected intramuscularly with

the first dose of recombinant hepatitis B vaccine (Euvax B; containing 20 µg purified HBsAg and 0.5 mg aluminum hydroxide gel).

Vaccines against hepatitis B are safe. The vaccination is associated with uncommon, typically mild, and temporary adverse events. The Global Advisory Committee on Vaccine Safety has confirmed the hepatitis B vaccine's excellent safety profile and continues to monitor this vaccine's safety.[10] However, the patient, in this case, experienced undesirable events after receiving the first dose of the recombinant hepatitis B vaccine and she was finally diagnosed with HSP. A similar case was reported in 2003 where a 28-year-old healthcare worker suffered from HSP after receiving a booster dose of recombinant hepatitis B vaccine (Engerix B; SmithKline Beecham).[11] Other cases of vasculitis after receiving the hepatitis B vaccine that have been reported so far include cutaneous vasculitis,[14] lymphocytic vasculitis,[15] cutaneous polyarteritis nodosa,[16] large artery vasculitis.[12] periarteritis nodosa,[17] and hypersensitivity vasculitis.[18]

Since it was feared that the condition would get worse, the patient was not given a second dose. This decision is based on a study conducted in 1999 in which, among 22 patients who developed rheumatic disorders following hepatitis B vaccination, the next hepatitis B vaccine inoculation was administered to 10 patients despite their complaints, and in eight cases, the complaints worsened.[19] This decision-making was strengthened by the results of anti-HBs of 94.42 mIU/mL. Anti-HBs could be measured to determine the immunity after B vaccination, with levels over 10 mIU/mL in 1 month after the last dose of the primary vaccination series considered reliable indicators of HBV protection. When immunocompetent kids and adults had anti-HBs concentrations of 10 mIU/mL or higher after vaccination, they were completely protected against both acute diseases and chronic infections (documented for 30 years), even if anti-HBs concentrations eventually dropped to less than 10 mIU/mL.[10]

Upper respiratory tract infections preceded many HSP cases, and a correlation between virtually all respiratory pathogens and HSP is suggested. The most frequently associated pathogens are Streptococcus strains and Parainfluenza virus.[20] In this instance, the ASTO result was less than 200, so it can be inferred that upper respiratory tract infection is not the culprit. Additionally, drugs prescribed by an otorhinolaryngologist have always been effective in controlling chronic tonsillitis that has been experienced thus far. Before receiving the hepatitis B vaccine, the patient had never experienced this before; thus, the vaccine is the most plausible explanation for this occurrence.

Vasculitis induced by antiviral vaccines and drugs is less common and less well-known.[21] The deposition of IgA1-dominant immune complexes in target organs is essential to the pathophysiology of HSP.[22] It is believed that IgA depositions in the blood vessel walls of the affected organs, especially the skin, digestive system, joints, and kidneys, cause clinical symptoms. However, the pathophysiology of HSP is not yet completely understood.[20] Sensitivity to one of the vaccine components, pseudoallergic reactions that frequently arise after hyperimmunization, and worsening of atopic disease or vasculitis can be categorized as vaccine-specific allergic reactions.[23] The question arises, namely, why the patient did not experience any untoward events after she received the hepatitis B vaccine at birth.

HSP diagnosis is based on clinical criteria.[20] The condition is uncommon in adults but has a more severe course.[22] The new EULAR/PRINTO/PRES criteria were published in 2010 and represent the gold standard for the diagnosis of HSP (**Table 2**). In children, the sensitivity is 100% and the specificity is 87%. One study analyzed the application of these criteria to adults and showed that they have a diagnostic sensitivity of 99.2% and a specificity of 88%, thus validating their usage for all patients with HSP.[20]

This patient met the mandatory criteria for making the diagnosis, namely purpura or petechiae with predominance in the lower limbs, and the presence of acute diffuse abdominal pain and arthralgia was also found. Gastrointestinal symptoms typically develop within a week of the appearance of the rash.[22] However, in this

patient, gastrointestinal symptoms manifested 5 days after the appearance of the rash as diffuse abdominal pain and fresh bloody stools. Joint involvement is transient and only involves the index finger of the patient's left hand. A skin biopsy, which is the gold standard for diagnosing cutaneous vasculitis, was not performed. This is because IgA-dominant vascular deposits are characteristic of HSP but are not sufficient to diagnose HSP, as these deposits could be found in other vasculitis syndromes, erythema nodosum, and conditions associated with venous stasis.[22]

The treatment of HSP in adults is still a subject of debate.[22] The patient in this case was treated with corticosteroids and mycophenolate. The utilization of corticosteroids in HSP patients is contentious. Mycophenolate is an immunosuppressive medication that can impede T and B cell growth and reduce antibody production. Its toxicological profile is excellent. Mycophenolate + low-dose prednisone is superior to full-dose prednisone, with the same remission rate, fewer adverse effects, and fewer relapses.[22] Additionally, the patient received folic acid and vitamin D3 supplements. Folate is necessary for regular cell reproduction and proliferation. Folate analogs have been and remain useful as antibiotics and cytotoxic medications in various diseases. Folate (vitamin B9) is an essential and underappreciated element having substantial direct and indirect effects on the body and a putative regulatory role in autoimmune and chronic inflammation.[25] Although the role of vitamin D in autoimmunity remained controversial, vitamin D has been widely recognized for reducing the risk of diabetes mellitus, depression, dementia, cancer, cardiovascular diseases, allergies, and asthma, as well as chronic infections.[26] In two case reports, vitamin D proved to be beneficial in autoimmune cases, namely helping to achieve remission of severe myasthenia gravis[27] and minimizing exacerbations of graves disease.[28]

In the course of treatment, the patient developed knee osteoarthritis, which was thought to be due to steroid use. In osteoarthritis itself, six major categories of modifiable risk factors have been identified: (1) obesity and overweight, (2) comorbidity, (3) occupational factors, (4) physical activity, (5) biomechanical factors, and (6) diet exposures.[29] Looking deeper, things that can also trigger the onset of osteoarthritis, in this case, are patients who are overweight, have a comorbidity, and have high physical activity. Therefore, the patient was sent to the medical rehabilitation department and underwent cryotherapy. Additionally, the patient is asked to routinely do stationary cycling. This combination gives better results than cryotherapy alone.[30] Stationary cycling may reduce pain and enhance the patient's athletic performance.[31]

Telogen effluvium that occurs in this patient is thought to be caused by an autoimmune condition suffered along with low levels of vitamin D in the blood. As it is known that vitamin D is essential for cell growth, its deficiency may also be a cause.[32] In addition to continuing treatment, minoxidil and topical corticosteroids were administered to help improve this condition. Minoxidil inhibits or induces the catagen phase of the hair follicles, whereas topical corticosteroid was administered because they have been proven to be an effective adjuvant therapy.[32]

Due to the insignificant increase in vitamin D3 yield, the patient was given 15.000 IU of vitamin D3 together with 90 mcg of vitamin K2 daily. We use the "Coimbra Protocol," in which vitamin D3 is administered at high levels to improve autoimmune illnesses. Orally administered vitamin D3 up to 1000 IU per kilogram of body weight is safe for calcium metabolism and renal function when strict dietary and fluid intake requirements are adhered to for up to 3.5 years. Vitamin K2 (menaquinone) has been described as a bone cofactor for mineralization, circulatory, and endothelial protective factors. Moreover, antioxidative effects have been outlined. Vitamin K2 is added to the "Coimbra Protocol" in quantities ranging from 100 to 800 mcg per day, to minimize the risk of calcification of arteries[26]. Because levels of serum calcium and urinary calcium excretion were not measured in this patient, we decided to use 90 mcg of K2. After 3 months of using high-dose vitamin D3 accompanied by K2, the level of serum vitamin D3 in this patient increased significantly until it reached optimal levels. Together with optimal

levels of vitamin D in the blood, the patient's complaints and allergies dissipate.

Based on several studies, tonsillectomy has also been proposed as a therapy and preventative measure for HSP, which is frequently precipitated by an upper respiratory tract infection.[20] In a retrospective study[33], from 78 children diagnosed with HSP, an upper respiratory tract infection was reported to occur in 32/78 (41%) children. It has been shown that HSP associated with chronic tonsillitis is mainly associated with streptococcal infection.[34] Because the patient had a history of chronic tonsillitis and had experienced exacerbations, she was referred to the ENT department, where a tonsillectomy was performed. After undergoing the surgery, the recurrence of HSP in our patient was eliminated. This is in line with a study where, compared with those of the non-surgery group, the complaints of the surgery group improved significantly after surgery.[34] Furthermore, there was a case of HSP nephritis that was successfully treated with tonsillectomy and steroid pulse therapy.[35] Moreover, there was a case report of clinical remission of HSP nephritis after a monotherapeutic tonsillectomy.[36]

CONCLUSION

Hepatitis B vaccination is one of the etiologies of HSP, although it is rare, so it is important to ask about the vaccination history in patients with suspected HSP. Correction of vitamin D and performing tonsillectomy provide better treatment results in HSP cases in this patient.

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CONFLICT OF INTEREST

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