Lichenoid drug eruption induced by rosuvastatin, a case report and review literatures

Angkana Norasetthada

Department of Internal medicine, rheumatology unit, Buddhachinaraj Phitsanulok Hospital, Thailand.

Abstract

Cutaneous drug reactions have a wide variety of clinical features. Lichenoid drug eruptions (LDE) are rare and it may be difficult to differentiate them from idiopathic lichen planus. Gold, quinine, quinidine and penicillamine are well-known inducers of such eruptions[1,2], but there are only a few reports of lichenoid eruption induced by 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statin)[2,3]. I described a lichenoid eruption linked to atorvastatin and rosuvastatin. His clinical features, in addition to histological findings, helped to establish the diagnosis. The cutaneous eruption resolved one month after the cessation of rosuvastatin. and a proposed alternative regimen to reduce total cholesterol (TC) and LDL-C in a patient with atherosclerotic heart disease.

For this case study, the patient gave written informed consent.

ผื่นแพ้ยาทางผิวหนังแบบไลเคนอยด์ที่เกิดจากยา rosuvastatin รายงานผู้ป่วยและทบทวนวรรณกรรม ผื่นแพ้ยาชนิดไลเคนอยด์พบได้ไม่บ่อย อาการทางคลินิกแยกได้ยากจากผื่นไลเคนนอยด์ปฐมภูมิ ยาที่ทำให้เกิดผื่นแพ้ชนิดไลเคนอยด์ ส่วนใหญ่เกิดจากยาทองคำ ควินีนและเพนนิซิลลามีน รายงานการเกิดผื่นแพ้ยาชนิดนี้จากยากลุ่มยับยั้งโคเอนไซม์ 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) (สแตติน) น้อยมาก รายงานผู้ป่วยฉบับนี้เกี่ยวกับการเกิดผื่นไลเคนอยด์ที่เชื่อมโยงกับ atorvastatin และ rosuvastatin และผื่นผิวหนังหายไปหนึ่งเดือนหลังจากการหยุด rosuvastatin และใช้สูตรทางเลือกการรักษาลดคลอเลสเตอรอลรวม (TC) และ LDL-C ในผู้ป่วยโรคหลอดเลือดหัวใจ

Keywords: lichenoid drug eruption, atorvastatin, rosuvastatin

To cite: Norasetthada A.
Thai J Rheum. 2025;2(3):36-42. Available from: https://he04.tci-thaijo.org/index.php/tjr

Case Report

A 61-year-old man came to rheumatology clinic at Buddhachinaraj Phitsanulok hospital due to suffering from a 15 months history of a bilateral numerous pruritic, violaceous papulous eruptions on his forearms, hands, thighs, trunk and scalp. (figure 1)There was neither mucosal nor nail involvement. He disclaimed having a fever, a viral infection that had occurred previously, arthritis, allergies, and any respiratory, gastrointestinal, or urinary symptoms, red eye, oral or genital ulcer.

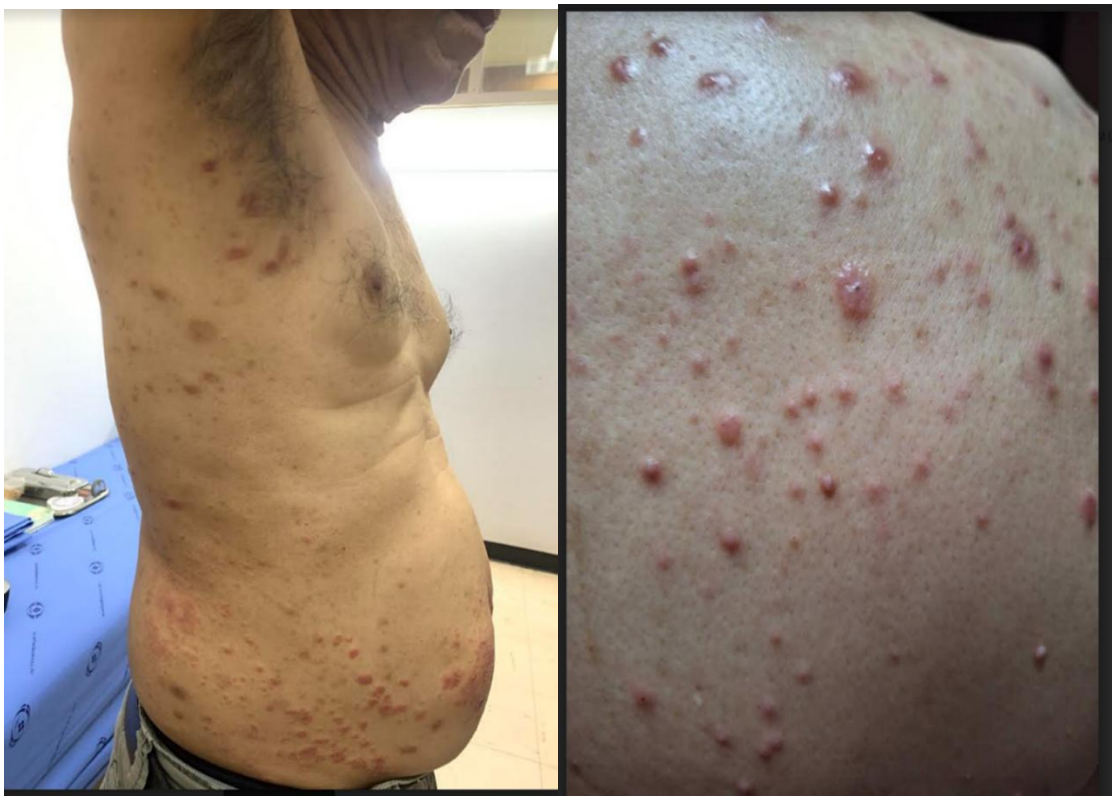
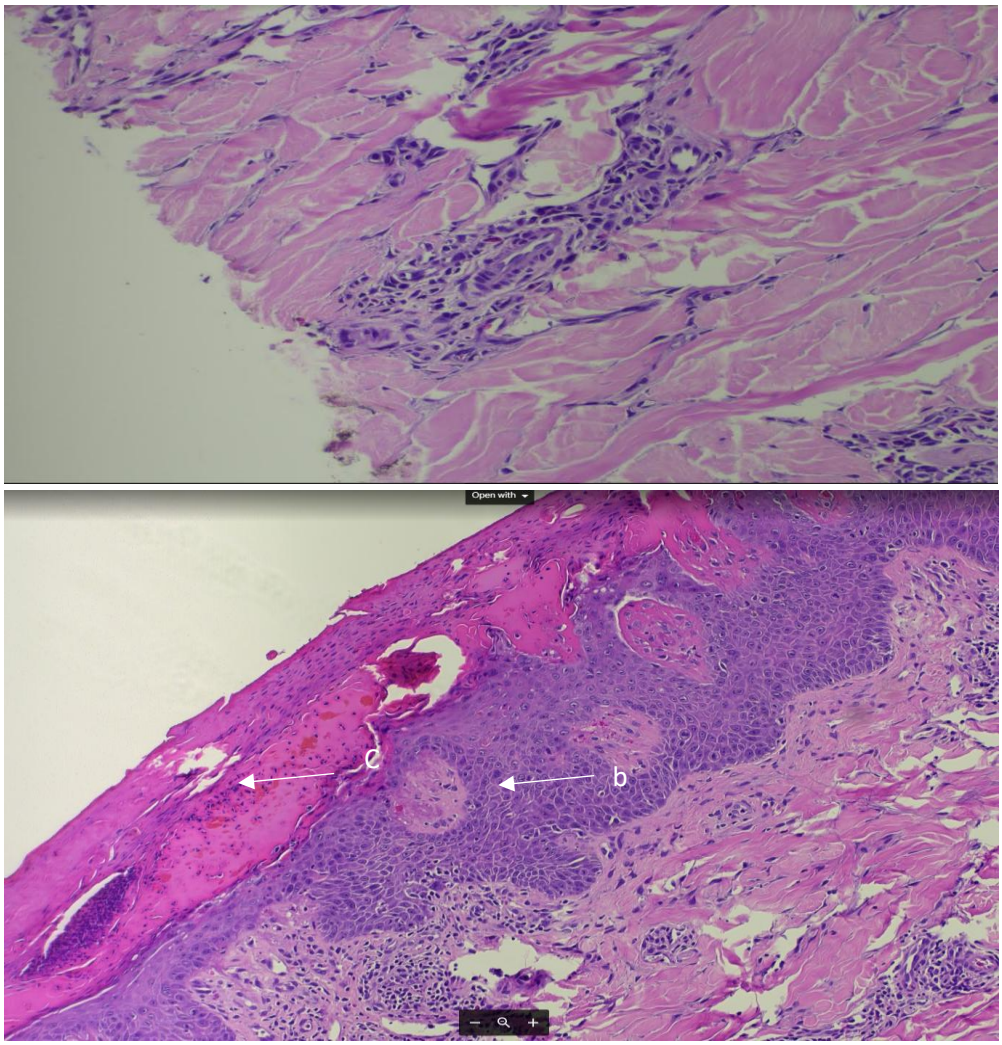


Figure 1. Multiple lentil sized, shiny, violaceous papules up to1 cm in size.

Physical examination revealed multiple lentil sized, shiny, violaceous papules up to1 cm in size. (Figure1) His body temperature was normal, his heartbeat was regular at 80 beats per minute, and his arterial blood pressure was 140/90 mmHg. There was no evidence of abdominal discomfort, lymphadenopathy, hepatosplenomegaly, or abnormal heart–lung or lymphatic examination results. His workup was normal for C-reactive protein 2.4 mg/dl (<5 mg/dl). The levels of complement component 3, and complement component 4 were all within normal ranges. Autoantibodies (anti-nuclear antibodies and antineutrophilic cytoplasmic antibodies), and serological testing for hepatitis B and C, and HIV virus were all negative. Hematuria, proteinuria, and granular casts were not detected in the urine analysis. Complete blood count including eosinophils , renal, and liver function test were within normal limit. The radiograph of the chest was normal. No more organs were impacted. Electrocardiography revealed normal sinus rhythm, no ST-T change, no chamber enlargement.

As of May 2021 he was diagnosed triple vessels atherosclerotic heart disease, status post percutaneous coronary intervention of right coronary artery. His medicines were atorvastatin, carvedilol, enalapril and clopidogrel. Four months later, on August 2022 he developed multiple pruritic erythematous papules. He received topical corticosteroids, anti- histamine, and short course of prednisolone, his lesions transient improved and flared up again about 3 times. Then atorvastatin was replaced by rosuvastatin on November 2022. His skin lesions continued grew up. He came to hospital and skin biopsy on 25 September 2023 revealed; perivascular dermatitis. The treatment he received were topical corticosteroids, anti- histamine, and short course of prednisolone twice a month. Until 29

Febuary 2024, at another hospital skin biopsy was done, and revealed: parakeratosis, spongiosis, irregular acanthosis in the epidermis, superficial infiltration with lymphocytes in the dermis. Histologic diagnosis was Spongiotic dermatitis. The treatment he received were multiple courses of topical corticosteroids, anti-histamine, and short course of prednisolone. His lesions briefly regressed and then rapidly grew up over and over. Then he developed diabetes mellitus on May 2024, and empagliflozin was prescribed. The lastest hospital he came performed skin biopsy again. The information he gave was allergic dermatitis, but he had no the histological result, and prescribed him a cyclosporine. He was frustrated about the diagnosis and cyclosporine side effects. Then he came to rheumatology clinic, Buddhachinaraj hospital. I suggested histological reviewing, he was not comfortable going back to request a biopsy from the previous hospitals and requested re-biopsy. Then the 4th skin biopsy was performed, and revealed: Vacuolar interface dermatitis, superficial and deep perivascular lymphocytic infiltrates with rare eosinophils and neutrophils. Acanthosis, spongiosis with parakeratosis and focal scale crust with neutrophils collection. No definite vasculitis was seen. (figure 2) Pathologist comment it was consistent with clinical drug eruption. The other differential diagnosis includes contact dermatitis, insect bite and other eczematous dermatitis. Rosuvastatin, enalapril, clopidogrel and carvedilol were stopped. I prescribed ezetimibe instead of rosuvastatin, diltiazem for carvedilol and enalapril, aspirin for clopidogrel. Four weeks later, he did't feel itchy at all and his skin lesion completely regressed. Then I rechallenged enalapril, and two weeks later no new lesion developed. Again, I rechallenged carvedilol, and two weeks later no new lesion developed. Next, Clopidogrel was rechallenged and no new lesion developed. My patient and his wife did't want to rechallenge rosuvastatin, and I absolutely agree with them. Finally his medications are ezetimibe, carvedilol, enalapril and clopidogrel.



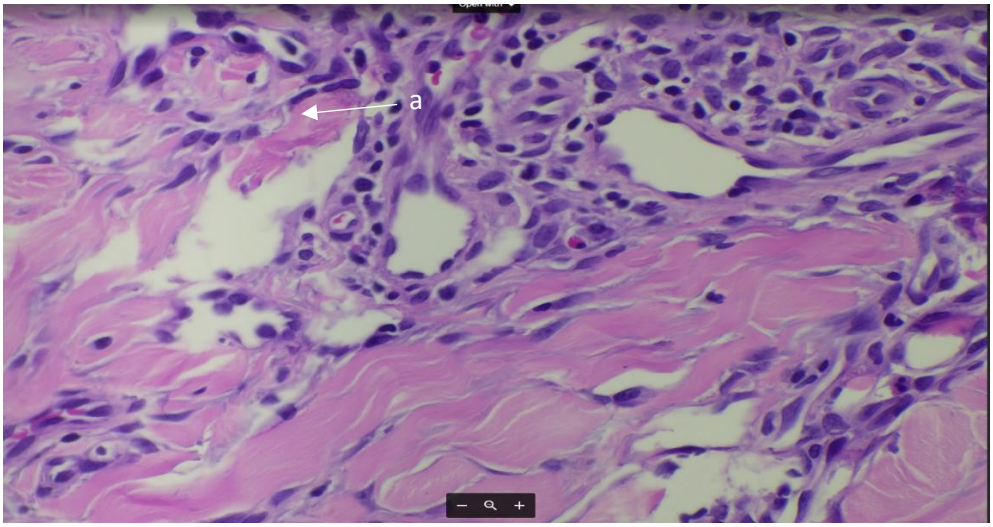


Figure 2. a) Vacuolar interface dermatitis, b). superficial and deep perivascular lymphocytic infiltrates with rare eosinophils and neutrophils. c). Acanthosis, spongiosis with parakeratosis.

Discussion

Lichen planus (LP) is an inflammatory, pruritic disease of the skin and mucous membranes, which can be either generalized or localized. It is characterized by distinctive purplish, flat-topped papules having a predilection for the trunk and flexor surfaces. On the surface often white stripes (Wickham's striae) might be visible. The lesions may be discrete or coalesce to form plaques. Histologically, there is a "saw-tooth" pattern of epidermal hyperplasia and vacuolar alteration of the basal layer of the epidermis along with an intense upper dermal inflammatory infiltrate composed predominantly of T-cell lymphocytes. The etiology is unknown. It occurs in the general population at a rate of 0.9-1.2 % and oral lesions may be seen in 30-70 % of these patients. It is diagnosed on clinical symptoms and biopsy can confirm the diagnosis. It is a self-limiting disease, but recovery might be slow an remission occurs in 1-2 years; oral lichen seems to follow a more chronic course, with a mean duration of 4.5 years[4,5]

Drug induced lichenoid eruptions (LDE) can differ in clinical (and histological) aspects from lichen planus; next to lichenoid elements, LDE may be accompanied with papular, scaling and eczematous lesions. The predilection sites are not different. Clinical correlation can be very useful. Key histologic features seen in LDE, that are not common in LP, include the presence of eosinophils and the presence of prominent parakeratosis. The two conditions can be differentiated only by the time course of skin or mucous membrane involvement in relation to drug administration and by re-challenging with the suspected agent.[6] In this patient both clinical and histologic finding were mostly compatible with LDE.

Frequently the lichenoid eruptions occur a few months after starting the drug, but the latency may very between days to several years. The time period from the commencement of the medication to onset of drug eruption ranged from 4 days to 7 years with a median of 3 months[7]. In this patient the latent time period of atorvastatin to onset of LDE was 4 months and still continuing after rosuvastatin was used.

The pathogenic mechanism of LDE is not well understood, a type IV allergy is sometimes involved. A dose dependency is suggested. Some drugs change surface antigens, whereas other drugs change enzyme systems. These aberrations may precipitate an immune response, in which cytotoxic CD8+ T cells are activated, which then cause epidermal damage[8,9]. For statins no specific mechanism was described.

LDE is most frequently related to β-blockers, captopril, penicillamine, hydrochlorothiazide, antimalarials, furosemide, quinidine, non-steroidal anti-inflammatory drugs, tetracycline, quinacrine, gold, sulfonylureas, hydroxyurea and methyldopa[10]. Although its pathogenetic mechanism is

incompletely understood, cell-mediated autoimmune reactions against basal layer keratinocytes are thought to be involved[10]. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (HMGCRi; statins) are frequently prescribed pharmaceutical products. Statins are the mainstay of the management of elevated low-density lipoprotein-cholesterol (LDL-C) levels in patients with high cardiovascular (CV) risk. Statin are well tolerated with a good safety profile.

The most commonly reported side effects of statins are myotoxicity and hepatotoxicity. Statins have also been associated with a number of cutaneous conditions. Common adverse skin reactions in this group are urticaria, eczema, dermatitis, skin eruption, pruritus, alopecia and angioneurotic edema. Beside these, several serious skin reactions are described. Lichenoid drug eruption caused by HMGCRi is exceptional.[11-17]

Case reports of LDE have been described in association with simvastatin,[18,19] pravastatin,[20,21] a torvastatin,[22,23] rosuvastatin,[24] fluvastatin and lovastatin.[25]

In patient who had developed LDE from simvastatin and then switched to rosuvastatin, the rash came back again.[24] And one case developed LDE due to fluvastatin and then switched to lovastatin the eruption recurred.[25] Active form of statins are structurally similarity, then LDE due to statin may be class effect. Nevertheless, establishing a relationship between a suspected agent and the adverse reaction was also complicated by multiple drug used in this patient. Since amlodipine,[26,27] clopidogrel[28], β-blocker[29-34] and enalapril[35-37] had been reported drug induced LDE. β-Blockers are noted to have the highest occurrence of adverse cutaneous reactions compared with any other antihypertensive medication.[29] Cross-reactivity among β -blocker agents has not been demonstrated, in five case reports of β -blocker induced LDE, no reaction was noted with an alternative - β blocker.[32-34]

Carvedilol had never been reported drug induced LDE, then I rechallenged carvedilol. Two weeks later no new lesion developed. Enalapril was the second drug that I rechallenged, and two weeks later no new lesion developed. Next, clopidogrel was rechallenged and no new lesion developed. Hence in this case, statin was highly likely to be the offending drug because changing atorvastatin to rosuvastatin be equal to rechallenge with another statin also caused lichenoid eruption. The temporal relationship also supported this hypothesis. and a proposed alternative regimen, rosuvastatin to reduce total cholesterol (TC) and LDL-C in this patient with ischemic atherosclerotic heart disease. Ezetimibe is cholesterol absorption inhibitor, indicated as first-line therapy in the case of proven intolerance to statins.[38]

Conclusion

Statins are generally used in the management of hypercholesterolemia; however, several adverse cutaneous events have been observed in patients treated with statins. LDEs are an uncommon adverse cutaneous event associated with statin medications. The new onset of lichenoid dermatitis in an individual receiving statin therapy should raise the concern that this skin eruption may be associated with the medication. LDE associated with statin therapy requires discontinuation of the statin. Active form of statins are structurally similarity, then LDE due to statin may be class effect, alternative class of medication for the treatment of hypercholesterolemia is usually necessary.

Reference

1. Halevy S, Shai A. Lichenoid drug eruptions. J Am Acad Dermatol 1993; 29: 249 – 255.
2. Keough GC, Richardson TT, Grabski WJ. Pravastatin induced lichenoid drug eruption. Cutis 2000; 61: 98-100.
3. Roger D, Rolle F, Labrousse F, Brosetti A, Bonnetblanc JM. Simvastatin-induced lichenoid drug eruption. Clin Exp Dermatol 1994; 19: 88 – 89.
4. Ellgehausen P, Elsner P, Burg G. Drug-induced lichen planus. Clin.Dermatol. 1998;16(3):325-32.
5. Thompson DF, Skaehill PA. Drug-induced lichen planus. Pharmacotherapy 1994;14(5):561-71.
6. Emanuel P, Oakley A. Lichenoid drug eruption. Clues to diagnosis in dermatopathology. Derm101.com (accessed 10 September 2018). https://dermnetnz.org/topics/lichenoid-drug-reaction-pathology
7. Mullins RJ, Lones R, Dutta B. Lichenoid drug eruption secondary to topical timolol and dorzolamide eye-drops. Australas J Dermatol 2004; 45:151-2.
8. Ellgehausen P, Elsner P, Burg G. Drug-induced lichen planus. Clin.Dermatol. 1998;16(3):325-32.
9. Thompson DF, Skaehill PA. Drug-induced lichen planus. Pharmacotherapy 1994;14(5):561-71.
10. Jain S.Dermatology Illustrated study guide and comprehensive board review.2nd ed.Springer; Switzerland: 2017. pp.106–109.
11. Dutch SmPC Lescol®. (version date: 1-11-2013, access date: 3-4-2014). http://db.cbgmeb.nl/IB-teksten/h18719.pdf.
12. Dutch SmPC Zocor®. (version date: 31-12-2013, access date: 3-4-2014) http://db.cbgmeb.nl/IB-teksten/h13193.pdf.
13. Dutch SmPC Lipitor®. (version date: 2-1-2014, access date: 3-4-2014). http://db.cbgmeb.nl/IB-teksten/h21081.pdf.
14. Dutch SmPC Selektine®. (version date: 30-4-2013, access date: 3-4-2014). http://db.cbg-meb.nl/IB-teksten/h13755.pdf.
15. Dutch SmPC Crestor®. (version date: 23-12-2013, access date: 3-4-2014). http://db.cbg-meb.nl/IB-teksten/h26872.pdf.
16. Dutch SmPC Vezepra®. (version date: 19-8-2012, access date: 22-4-2014). http://db.cbg-meb.nl/IB-teksten/h103422.pdf.
17. Dutch SmPC Livazo®. (version date: 19-8-2012, access date: 22-4-2014). http://db.cbgmeb.nl/IB-teksten/h103768.pdf.
18. Roger D, Rolle F, Labrousse F, Brosset A, Bonnetblanc JM. Simvastatin-induced lichenoid drug eruption. Clin.Exp.Dermatol. 1994;19(1):88-9.
19. Stoebner PE, Michot C, Ligeron C, Durand L, Meynadier J, Meunier L. Simvastatin induced lichen planus pemphigoides. Ann.Dermatol.Venereol. 2003;130(2 Pt 1):187-90.
20. Keough GC, Richardson TT, Grabski WJ. Pravastatin-induced lichenoid drug eruption. Cutis 1998;61(2):98-100.
21. Pua VS, Scolyer RA, Barnetson RS. Pravastatin-induced lichenoid drug eruption. Australas.J.Dermatol. 2006;47(1):57-9.
22. Forouzan P, Riahi RR, Cohen PR. Atorvastatin-induced Lichenoid Drug Eruption: A Case Report and Review of Statin-associated Cutaneous Adverse Events Cureus 12(3): e7155. https://doi.org/10.7759%2Fcureus.7155
23. Vesza Z, Pires C, Pedro Marques da Silva. Statin-related Lichenoid Dermatosis: An Uncommon Adverse Reaction to a Common Treatment. https://doi.org/10.12890%2F2018_000844.
24. Wong ITY, Huang Y, Zhou Y. Drug Eruption to Rosuvastatin With Recurrence on Simvastatin: A Case Report. Journal of cutaneous medicine and surgery.Volume 22, Issue 3:359-361. https://doi.org/10.1177/1203475418756376
25. Sebok B, Toth M, Anga B, Harangi F, Schneider I. Lichenoid drug eruption with HMGCoA reductase inhibitors (fluvastatin and lovastatin). Acta Derm.Venereol. 2004;84(3):229-30.

26. Lakshmi C,Srinivas C R, Ramachandran B, Pillai SB, Nirmala V.Perforating lichenoid reaction to amlodipine.. Indian J Dermatol. 2008; 53(2): 98–99.
27. How OJ, Muhamad R, Muthusamy R, Rahman FA, Zulkifl MM, Amlodipine-induced lichenoid drug eruption: A case report. Bangladesh Journal of Medical Science. 2023; 22(1): 229-233.
28. Guijarro BG, Sánchez L. Lichenoid reaction caused by Clopidogrel, a new anti-platelet drug. Med Oral. 2003;8(1):33-7.
29. Upadhayai JB, Nangia AK, Mukhija RD, et al. Cutaneous reactions due to antihypertensive drugs. Indian J Dermatol 2006; 51: 189-91
30. Mullins RJ, Lones R, Dutta B. Lichenoid drug eruption secondary to topical timolol and dorzolamide eye-drops. Australas J Dermatol 2004; 45: 151-2
31. Bodmer M, Egger SS, Hohenstein E, et al. Lichenoid eruption associated with the use of nebivolol. Ann Pharmacother 2006; 40 (9): 1688-9
32. Gange RW, Jones EW. Bullous lichen planus caused by labetalol. BMJ 1978;1 (6116): 816-7.
33. Beckman KA, Chanes L, Kaufman SR. Lichen planus associated with topical beta-blocker therapy. Am J Ophthalmol 1995; 4: 530-1.
34. O'Brien TJ, Lyall IG, Reid SS. Lichenoid eruption induced by sotalol. Australas J Dermatol 1994; 35: 93-4.
35. Firth AN, Reade CP. Angiotensin-converting enzyme inhibitors implicated in oral mucosal lichenoid reactions. Oral Surg Oral Med Oral Pathol. 1989; 67: 41-44.
36. Vollenweider SR, Mainetti C, Donath R, Saurat JH. Enalapril-induced lichen planus-like eruption. J Am Acad Dermatol. 1995; 32 (2): 293-295.
37. Ruiz VR, Blasco MJ, Linares SJ, Serrano OS. Lichen planus-like eruption due to enalapril. JEADV. 2003; 17: 601-619.
38. Barrios V, Escobar C, Cicero AF, Burke D, Fasching P, Banach M, Bruckert E. A nutraceutical approach (Armolipid Plus) to reduce total and LDL cholesterol in individuals with mild to moderate dyslipidemia: review of the clinical evidence. Atheroscler Suppl. 2017;24:1–15.