Cutaneous hyperpigmentation induced by daclatasvir, sofosbuvir, and ribavirin combination therapy.

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ABSTRACT:

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A 61-year-old Thai man, with hepatitis C (HCV)-related cirrhosis, who underwent liver transplantation, presented with a 3-month history of generalized skin darkening. He had been treated with daclatasvir (DCV), sofosbuvir (SFV) and ribavirin (RBV) combination therapy for three months before developing skin hyperpigmentation accompanying by nail lunular and oral mucosal hyperpigmentation. The cutaneous pigmentation started to fade two months after drug discontinuation. Other investigations showed no evidences of systemic diseases contributing to cutaneous hyperpigmentation.

DCV/SFV/RBV combination has been used as a new treatment for hepatitis C virus. The reported adverse skin reactions from DCV/SFV/RBV are still limited, yet including erythema multiforme and Stevens-Johnson syndrome. At present, there is no reported case of skin hyperpigmentation after using these medications. We describe the first case of cutaneous hyperpigmentation induced by DCV/SFV/RBV combination.

Keywords: daclatasvir, sofosbuvir, ribavirin, drug-induced pigmentation.

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บทคัดย่อ:

นริศา บราวเนล, ชนัทธ์ กำธรรัตน์ รายงานผู้ป่วยสีผิวเข้มขึ้น หลังได้รับการรักษาด้วยยาดาคลาทาสเวียร์, โซฟอสบูเวียร์ และไรบาวิริน วารสารโรคผิวหนัง 2560; 33: 173-179.

สาขาวิชาตจวิทยา ภาควิชาอายุรศาสตร์ โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

ผู้ป่วยชายอายุ 61ปี ได้รับการวินิจฉัยเป็นโรคตับแข็งจากการติดเชื้อไวรัสตับอักเสบซี เข้ารับการรักษาด้วยการปลูกถ่ายตับ มาด้วยอาการสำคัญคือสีผิวเข้มขึ้นทั่วๆ 3 เดือนก่อน ผู้ป่วยได้รับการรักษาภาวการณ์ติดเชื้อไวรัสตับอักเสบซีด้วยยาต้านไวรัส เป็นยาร่วมได้แก่ ดาคลาทาสเวียร์ (daclatasvir; DCV), โซฟอสบูเวียร์ (sofosbuvir; SFV) และ ไรบาวิริน (ribavirin; RBV) โดยหลังได้ยา 3 เดือน สังเกตว่าสีผิวทั้งตัวเข้มขึ้น ตรวจร่างกายพบสีผิวเข้มขึ้น ทั่วๆ เด่นที่บริเวณใบหน้า มือ และเท้า เล็บสีเข้มขึ้น ร่วมกับพบจุดดำที่ริมฝีปาก และลิ้น หลังจากหยุดยาดังกล่าวได้ประมาณ 2 เดือนพบว่าผิวที่คล้ำเริ่มดีขึ้น

ยาร่วม DCV/SFV/RBV เป็นยาสูตรใหม่ที่ใช้ในการรักษาการติดเชื้อไวรัสตับอักเสบซี อาการข้างเคียงทางผิวหนังที่มีรายงานในปัจจุบันมีค่อนข้างจำกัดที่มีรายงานคือ erythema multiforme และ ผื่นแพ้ยารุนแรงชนิด Stevens-Johnson syndrome แต่ยังไม่พบรายงานการเกิด ผิวสีเข้มขึ้นจากการใช้ยาร่วมลักษณะนี้มาก่อน รายงานฉบับนี้นำเสนอผู้ป่วยรายแรกที่มีสีผิวเข้มขึ้นหลังได้รับยาร่วม DCV/SFV/RBV

คำสำคัญ : ดาคลาทาสเวียร์, โซฟอสบูเวียร์, ไรบาวิริน, ผิวสีเข้มขึ้นจากการใช้ยา

Case synopsis

A 61-year-old Thai man presented with asymptomatic, yet progressive skin darkening on the face, ears, dorsal aspect of forearms and legs for 3 months. His Fitzpatrick skin type was IV. His fingernails and toenails were also affected. He was diagnosed with hepatitis C (HCV)-related cirrhosis for two years and had undergone liver transplantation 7 months ago. Shortly after the transplantation, he received combination of antiviral drugs consisted of daclatasvir (DCV), sofosbuvir (SFV) plus ribavirin (RBV). He had been taking these drugs for approximately three months when he noticed that his skin became darker.

His HCV genotype was 3 and HCV RNA level before therapy was 341,072 IU/ml. He denied history of other medications. His current medications were as follows: tacrolimus 2 mg/d, mycophenolic acid 360 mg/d and lamivudine 100 mg/d. These drugs were started six months before the skin changes and were being continued until present. He denied any systemic symptoms, such as fatigue, hyperactivity or weight loss.

On physical examination, generalized brownish skin hyperpigmentation predominantly on the face and acral parts were noted (Figures 1, 2). Lunular hyperpigmentation and multiple longitudinal melanonychia of fingernails and

toenails were also noted (Figures 3, 4). Irregular brownish macules and patches on the mucosa of lower lip and dorsum of the tongue were seen (Figures 5, 6).

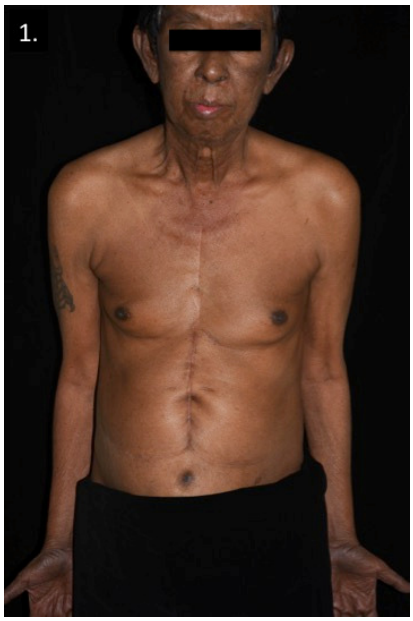

Figure 1

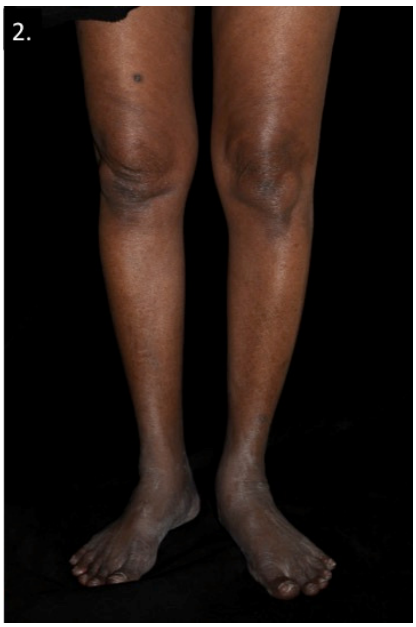

Figure 2

Figure 3

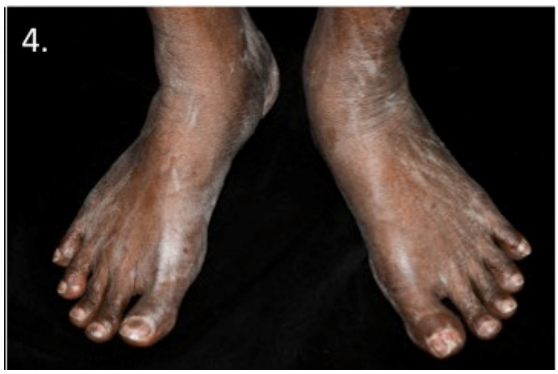

Figure 4

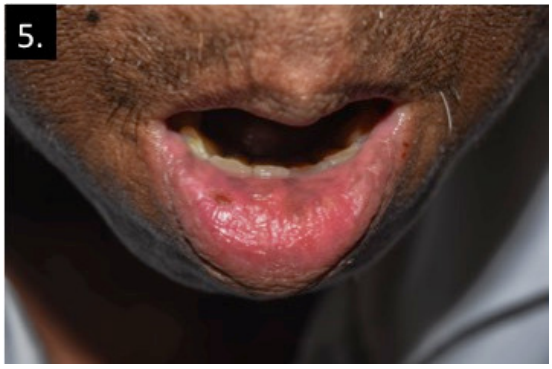

Figure 5

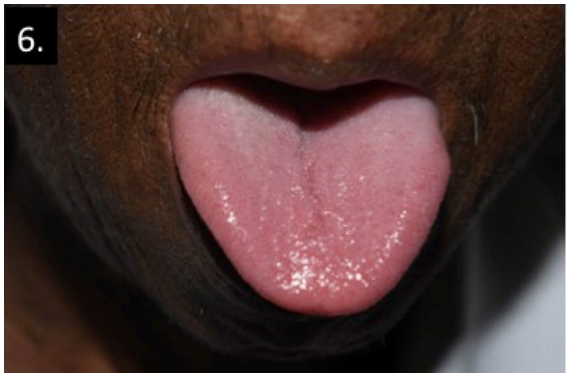

Figure 6

Further laboratory investigations including complete blood count, liver function tests, serum morning cortisol, ACTH, thyroid function tests, folate level, vitamin B12 level were all within normal limits. Serum ferritin was 756 ng/ml (30-400 ng/ml).

Two months after the completion of 24-week-DCV/SFV/RBV therapy, there was complete fading of lunular hyperpigmentation of fingernails (Figures 7, 8). Partial improvement of skin and nails hyperpigmentation were noted.

Discussion

Acquired generalized hyperpigmentation of skin, nails and mucosa is a result of increased melanin production and/or substance deposition in either epidermis or dermis. The differential diagnoses should include Addison's disease, hyperthyroidism, hemochromatosis, erythema dyschromicum perstans, megaloblastic anemia and drug-induced hyperpigmentation.[1] The common, well-established medications causing skin hyperpigmentation consist of antimalarial drugs, amiodarone, psychotropic drugs, zidovudine, tetracycline and heavy metals.[2]

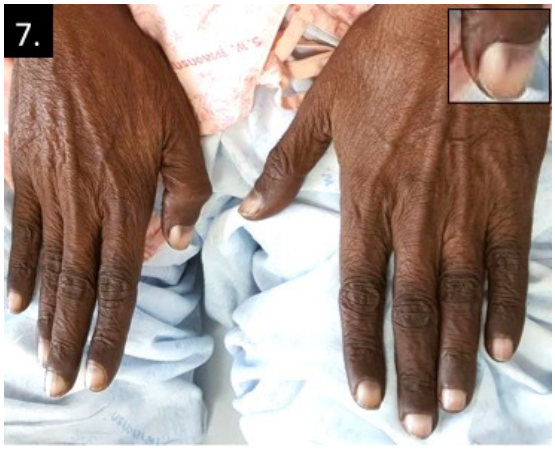

Figure 7

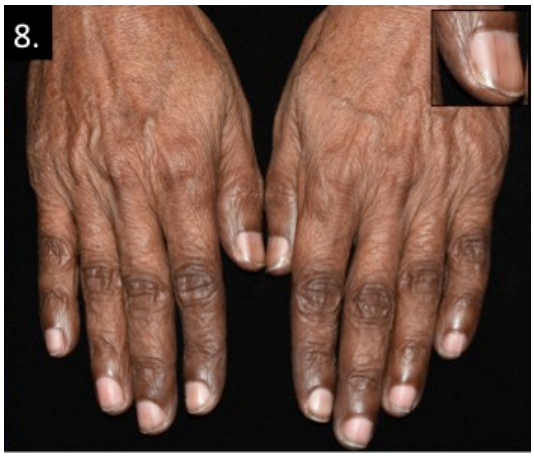

Figure 8

In our case, laboratory investigations for systemic disease causing cutaneous hyperpigmentation were so far normal. We excluded acquired hemochromatosis in the first place due to negative history of frequent blood transfusions and the improvement of his skin pigmentation without specific treatment.

Elevated serum ferritin can be related to various conditions such as, iron overload in hemochromatosis (2000-8000 ng/ml), damage to ferritin-rich tissues in liver diseases or other inflammatory diseases (500-2000 ng/ml).[3] Hence increased ferritin levels in our patient could be explained by his underlying liver disease. His cutaneous pigmentation was changed according to the period of the combined medications used, however, it is difficult to differentiate that DCV/SFV/RBV combination or DCV, SFV, RBV alone are responsible to cutaneous hyperpigmentation. Although he had received tacrolimus, mycophenolic acid, and lamivudine for six months before he developed skin darkening, it's unlikely that those drugs are responsible to his skin change since there was an improvement of his skin pigmentation while those drugs were being continued. Moreover, none of these drugs were known to cause skin pigmentation change. We concluded that his skin change was likely affected by DCV/SFV/RBV combination. Nevertheless, closed follow up of the disease progression is mandatory to confirm our diagnosis.

The pathogenesis of drug-induced pigmentation is not clearly understood. Clinical manifestations of drug-induced skin discoloration are often more pronounced on sun-exposed parts of the body. It was believed to be a result of either ultraviolet-induced melanin synthesis or transformation of drug into visible particles.[1] Interestingly, there is no rational explanation regarding the associated mucosal hyperpigmentation in the literatures. The diagnosis is usually made by temporal association that is appearance and fading of pigmentation after the use and cessation of suspected drug, respectively.

DCV and SFV, which are both new direct antiviral drugs for treating HCV infection, act as non structural protein 5B (NS5B) and NS5A inhibitors respectively.[4] The dermatological adverse effects from DCV and SFV are limited. Although there are few reported cases of erythema multiforme and Stevens-Johnson syndrome after using these medications, cutaneous hyperpigmentation has never been reported.[5]

RBV is an antiviral drug which acts as a nucleoside inhibitor. The combination of interferon-alpha (IFN-α) and RBV had been reported to cause skin and oral hyperpigmentation commonly in patients with dark skin types.[6,7] Most authors believe that IFN-α mainly plays part in the increased melanin production through upregulation of alpha-melanocyte stimulating hormone receptor expression. Interestingly, there is no reported case of cutaneous hyperpigmentation who received either IFN-α or ribavirin alone. It is more logical to conclude that IFN-α and ribavirin

combination therapy results in skin pigmentation rather than IFN-α or ribavirin monotherapy.

Zidovudine is a nucleoside analogue similar to RBV. Anecdotally, zidovudine is associated with cutaneous hyperpigmentation.[8,9] The study of mouse model for zidovudine-induced hyperpigmentation by Obuch et al., published in 1992, found that the increased pigmentation was due to increased melanosome production.[10]

SFV is a nucleotide analogue which consists of a sugar ring and a nitrogen base, structurally similar to that of zidovudine. We hypothesize that its mechanism of pigmentation may be similar to zidovudine. However, DCV contains no related molecular structure. The mechanism of pigmentation thus, remains a question. (Figure. 9)

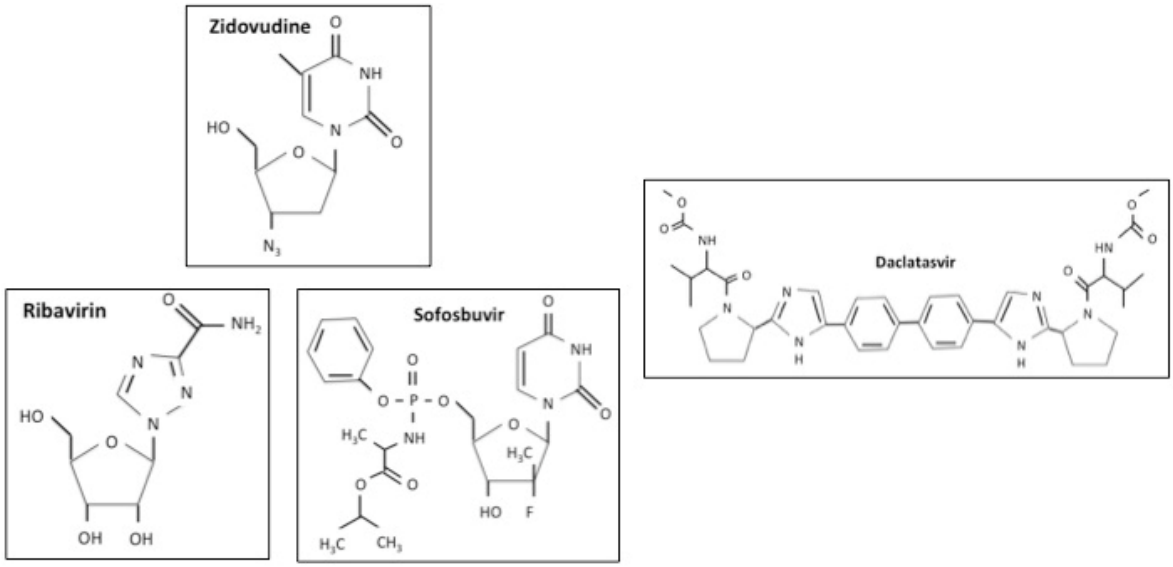

Figure 9 Molecular structure of zidovudine, SFV, DCV, and RBV[11]

In summary, we report the first case of suspected DCV/SFV/RBV combination-induced nail, mucosa and skin hyperpigmentation in HCV-related cirrhosis post liver transplantation. Further studies should be conducted for prevalence and the mechanism of drug-induced hyperpigmentation.

กิตติกรรมประกาศ

ผู้นิพนธ์ขอขอบพระคุณศาสตราจารย์นายแพทย์ประวิตร อัศวานนท์ ที่กรุณาช่วยตรวจแก้ไขความถูกต้องและตรวจทานภาษาของรายงานฉบับนี้จนเสร็จสมบูรณ์

References

1. Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. Am J Clin Dermatol 2001;2:253-62.

2. Krause W. Drug-induced hperpigemntation: a systematic review. J Dtsch Dermatol Ges. 2013;11:644-51.
3. Finch CA, Bellotti V, Stray S, et al. Plasma ferritin determination as a diagnostic tool. West J Med 1986;145:657-63.
4. Gamal N, Gitto S, Andreone P. Efficacy and Safety of Daclatasvir in Hepatitis C: An Overview. J Clin Transl Hepatol 2016;4:336-44.
5. Wang Y, Liu P. A case of erythema multiforme drug eruption associated with erythrodermic psoriasis induced by sofosbuvir and daclatasvir. J Clin Pharm Ther 2017;42:108-10.
6. Tsilika K, Tran A, Trucchi R, et al. Secondary hyperpigmentation during interferon alfa treatment for chronic hepatitis C virus infection. JAMA Dermatol. 2013;149:675-7.
7. Weng Y, Tsan M. Interferon and ribavirin-induced oral hyperpigmentation in two Taiwanese patients: case report and literature review. Clin Med Rev Case Rep 2015;2:067.
8. Terheggen F, Frissen J, Weigel H, Schouten I, Brinkman K. Nail, hair and skin hyperpigmentation associated with indinavir therapy. AIDS 2004;18:1612.
9. Singh SK, Rai T. A case of zidovudine induced pigmentation on palms and soles. Indian Dermatol Online J 2014;5:98-9.
10. Obuch ML, Baker G, Roth RI, Yen TS, Levin J, Berger TG. Selective cutaneous hyperpigmentation in mice following zidovudine administration. Arch Dermatol 1992;128:508-13.
11. Zidovudine, Ribavirin, Sofosbuvir, Daclatasvir [internet]. [cited 2017 May 26] . Available from: https://en.wikipedia.org/wiki/Zidovudine, https://en.wikipedia.org/wiki/Ribavirin, https://en.wikipedia.org/wiki/Sofosbuvir, https://en.wikipedia.org/wiki/Daclatasvir.