

Lichenoid type cutaneous hyperpigmentation induced by nebivolol

Nebivolole baęlı likenoid tip kutanöz hiperpigmentasyon

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Summary– Cutaneous hyperpigmentation is a common and well-defined side effect of many drugs, such as non-steroidal anti-inflammatory drugs, beta-blockers, and tetracyclines, but to the best of our knowledge there is no case of skin discoloration related to nebivolol in the literature. Presently described is lichenoid type cutaneous hyperpigmentation in a 46-year-old female patient. Hyperpigmentation emerged 3 months after initiating use of nebivolol and resolved after cessation of drug use. It was concluded that effect emerged as result of therapeutic doses of nebivolol.

Özet– Kutanöz hiperpigmentasyon steroid dışı antiinflamatuar ilaçlar, beta blokerler ve tetrasiklinler gibi birçok ilacın sık ve iyi tanınan bir yan etkisidir. Bildiğimiz kadarıyla literatürde nebivolole baęlı ciltte renk deęişikliği olan herhangi bir olgu yoktur. Bu yazıda, nebivolol kullanmaya başladıktan üç ay sonra ortaya çıkan ve ilacı kestikten sonra azalan likenoid tip kutanöz hiperpigmentasyonlu 46 yaşında bir kadın olgu sunuldu. Bu durumun terapötik dozlarda kullanılan nebivolol tedavisine baęlı olduğunu düşündük.

Nebivolol is a third-generation beta-blocker (BB) agent selective for beta1 receptors and is commonly used in patients with systolic heart failure and arterial hypertension (HT). Although severe bradycardia and atrioventricular nodal block are well-known side effects, fatigue, headache, dyspnea, insomnia, and dizziness are also defined as rare adverse effects of nebivolol.^[1] Cutaneous hyperpigmentation is skin discoloration that may have various causes, including infection, autoimmune disease, contact dermatitis, photosensitivity, and allergic reaction. Drug eruption is another possible cause of skin pigmentation. It is important to identify the drug responsible for the reaction, as withdrawal of the culprit medication is the only treatment in such cases. In this case, etiology of hyperpigmentation in 46-year-old female patient was clinically investigated for 1 year before nebivolol, which had been prescribed for HT, was finally diagnosed as source.

Abbreviations:

BB Beta-blocker
HT Hypertension

CASE REPORT

A 46-year-old female patient with no past medical history had been diagnosed with HT and prescribed 5 mg of nebivolol daily 15 months earlier. The patient was not using any other medication, and blood pressure levels remained in normal range during follow-up. At 3-month follow-up, the patient complained of erythematous eruptions on sun-exposed areas of her body, such as the face, hands, and neck; other areas were spared. Physical examination revealed symmetric eruptions of flat-topped, violaceous papules, often grouped and confluent, on the face, neck, and hands. All other physical findings, as well as blood biochemistry, hemogram, and urine analysis, were normal. There was no fever, and no other clinical symptoms or signs of systemic disease were present. The patient did not have history of any disease other than HT. Consultation with dermatology clinic was arranged. Clinical diagnosis was suggestive of hypersensitivity reaction to sunlight. Hyperpigmentation had been

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present for 1 year and persisted, though the patient had been protected from sunlight for previous 6 months. All possible causes of cutaneous hyperpigmentation, including connective tissue diseases (especially lupus erythematosus) were investigated in detail. No etiology consistent with this diagnosis was verified other than nebivolol usage for HT during this period. Histopathological examination of skin biopsy taken from hyperpigmented regions revealed interface dermatitis with band-like lymphocytic infiltrate, lichenoid type cutaneous hyperpigmentation in the basal cell layer, pigment incontinence within the dermis, and accumulation of pigment-laden macrophages around blood vessels and eccrine glands, all of which were consistent with drug-induced eruption. Nebivolol was considered potential cause and use was terminated. Angiotensin-converting-enzyme inhibitor (ramipril) was administered for HT. Lesions subsided about a month after cessation of the drug and totally disappeared within 3 months. No recurrence of lesions was observed in follow-up. The patient provided written consent to publication of information.

DISCUSSION

Present case is a very rare instance of nebivolol-induced lichenoid hyperpigmentation in sun-exposed areas of the body. BB agents have been used in the treatment of HT for many years. Among these agents, nebivolol, a third-generation BB, is different, due to high beta1 selectivity, vasodilator, and endothelium-dependent antioxidant properties.^[2] These advantages make nebivolol a strong alternative to other BBs, especially in specific patient populations, such as patients with asthma or chronic obstructive pulmonary disease, or those who experience erectile dysfunction when using other BBs.^[2] It is approved for treatment of stage 1 and 2 HT, and is generally well tolerated. It is contraindicated, however, in cases of severe bradycardia, atrioventricular nodal block other than first degree, cardiogenic shock, decompensated heart failure, and severe hepatic disease.

Hyperpigmentation is the darkening of an area of skin or nails caused by increased melanin. It can be result of sun damage, inflammation, or other skin injuries. Drug side effect is also an important cause of cutaneous hyperpigmentation, and it is important to identify drugs that induce this kind of reaction, as in most of cases, the only therapy is to withdraw the

culprit drug. The number of drugs capable of producing drug eruption is very large. Most are non-steroidal anti-inflammatory drugs and non-opioid analgesics, sulphonamides, and tetracyclines.^[3] Relationship between BB agents and skin eruptions has been reported in the literature many times.^[4] Clinical features and characteristics of these eruptions are variable and include psoriasiform, maculopapular and lichenoid types.^[5] There have been previous reports of adverse skin reactions, such as allergic contact dermatitis and generalized pruritis, associated with nebivolol treatment. Fedele et al.^[6] described case of 60-year-old woman who suffered from eczematous lesions in the periorbital areas and generalized pruritis for 3 years. Finally, nebivolol, used for 4 years due to mild HT, was determined to be cause of systemic contact dermatitis. That patient's complaints appeared 1 year after initiating nebivolol use. In our case, there was lichenoid hyperpigmentation, rather than eczematous lesions and accompanying pruritis, on sun-exposed areas of the whole body after just 3 months of nebivolol treatment. In addition, Bodmer et al.^[7] reported lichenoid eruption associated with use of nebivolol in 2006. However, in that case, eruptions occurred on both the extremities and the back of the patient, but not the sun-exposed areas of the body. In our case, the lichenoid eruptions had different characteristic of occurring as a form of phototoxicity. Lichenoid reactions on sun-exposed areas have been reported after exposure to hydrochlorothiazide, enalapril, fenofibrate, and furosemide, all commonly prescribed in treatment of cardiovascular disease. Eruption resolves spontaneously a few weeks to a few months after discontinuation of the offending drug. Treatment with corticosteroids may be warranted in patients who cannot discontinue the offending drug or have symptomatic or extensive disease.

Although there is close relationship between BBs and adverse skin reactions, this is the first case in the literature describing lichenoid type cutaneous hyperpigmentation as a form of phototoxicity induced by nebivolol. In this case, alternative diagnoses, such as idiopathic lichen planus, systemic connective tissue disease, cutaneous forms of lupus erythematosus, lichenoid contact reaction, and hepatobiliary disease, could be excluded due to the history of the patient, clinical picture, biopsy findings, and time course of the skin lesions.^[8] Ultimately, it was concluded that nebivolol may cause lichenoid cutaneous hyperpig-

mentation. Therefore, in patients using nebivolol, this side effect should be kept in mind. Treatment for this troublesome condition is to discontinue use of the drug.

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Anahtar sözcükler: Beta bloker; kutanöz hiperpigmentasyon; likenoid; nebivolol; yan etki.