

PYRIDOXINE INDUCED ROSACEA-LIKE DERMATITIS

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SUMMARY – Rosacea is a common chronic inflammatory cutaneous disease of unknown etiology, characterized by remissions and exacerbations, presenting with centropacial erythema and telangiectasias. It affects mainly adults around the age of 30 years and classically predominates in females. The pathophysiology of rosacea has not yet been fully understood. Risk factors are positive family history, very light skin phototype, sun exposure and consumption of spicy food or alcohol. Recently, there has been some evidence that some drugs or vitamins could be potential factors that can aggravate rosacea or induce rosacea-like symptoms. In this context, we present a 53-year-old female developing rosacea-like dermatitis due to a fixed combination of isoniazid and pyridoxine, which she was receiving along with rifampicin for the treatment of pulmonary tuberculosis.

Key words: *Pyridoxine; Vitamin B6; Rosacea – chemically induced*

Introduction

Rosacea is a common chronic inflammatory skin disease affecting blood vessels and pilosebaceous units. It mainly affects the central area of the face, presenting with many different clinical features. Rosacea occurs in adults, usually between 30 and 50 years of age, appearing more often in women. It is one of the most common diagnoses in the clinical dermatologic practice. The pathophysiology of rosacea has not yet been fully understood. Family history of the disease and very light skin phototype are among the most important risk factors. Moreover, some drugs are found to aggravate rosacea or induce rosacea-like symptoms. Herein, we report a 53-year-old female developing rosacea-like skin lesions due to a fixed combination of isoniazid and pyridoxine, which she was receiving along with rifampicin for pulmonary tuberculosis.

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Case Report

A 53-year-old female was referred to our Department for dermatologic evaluation of centropacial erythema with disseminated erythematous papular lesions. Clinical symptoms were of three-day duration with a tendency of progression, accompanied by intensive itching and pain. Seven months prior to the examination, pulmonary tuberculosis had been diagnosed and the patient had received four drugs as a first-line antituberculous regimen, including a fixed combination of isoniazid (INH) and pyridoxine, rifampicin, ethambutol and pyrazinamide for three months, followed by dual therapy consisting of isoniazid (INH) and B6 in fixed combination and rifampicin given simultaneously. Prior to the initiation of isoniazid, N-acetyltransferase type 2 genotyping was performed to personalize the dose, which showed slow acetylator phenotype. Consequently, lower doses of medication were prescribed, including 300 mg of isoniazid and 18.75 mg of pyridoxine every other day.

Clinical examination revealed diffuse centropacial erythema with evident erythematous papules without

telangiectasias (Fig. 1). Subjective symptoms of skin itching and sensitivity were also present. The patient's general condition was unremarkable, although she suffered from occasionally intermittent fever and mild chest pain. Recent sun exposure and application of topical corticosteroids were excluded. Family and personal history in a sense of facial flushing and sensitivity was negative. Considering clinical presentation that was highly suggestive of rosacea and reports describing association of pyridoxine intake and rosacea-like dermatitis, we decided not to perform skin biopsy. Furthermore, since pyridoxine is part of antituberculous therapy, we were not able to discontinue the use of the incriminated agent. Topical metronidazole and cold compresses were administered twice daily and the patient was advised to follow mandatory photoprotection. On post-therapeutic follow up examination two weeks later, the lesions started to diminish, as well as the patient's symptoms of sensitivity and pain (Fig. 2). Rapid complete regression was seen after discontinuation of isoniazid (INH) and pyridoxine therapy three months later.

Discussion

Rosacea is a common chronic inflammatory cutaneous disease of unknown etiology. Identified triggers are genetic predisposition, very light skin phototype

and external factors such as sun and high temperature exposure and diet¹. Additionally, drugs and vitamins could also be possible triggers for rosacea-like dermatitis²⁻⁶, including topical corticosteroids³ and immunomodulators², epidermal growth factor receptor (EGFR) inhibitors⁶, phosphodiesterase-5 inhibitors⁵ and vitamin B^{4,7-9}. Although the exact mechanism of drug induced rosacea still remains unknown, nitric oxide and prostaglandins are factors that could cause vascular alterations inducing rosacea^{5,7,8}. Furthermore, due to prolonged therapy with the incriminated drug, another potential factor could be irritation of the follicular epithelium leading subsequently to an inflammatory reaction^{4,7}. Some researchers suggest that drug induced rosacea-like dermatitis occurs in genetically predisposed individuals^{5,7}, and vitamin B induced rosacea appears to be more common in women⁷. Concerning vitamin B inducing rosacea, few cases have been reported so far⁷⁻⁹. Vitamin B3 (niacin) has been associated with skin flushing^{4,7-12}, whereas vitamins B2 (riboflavin), B6 (pyridoxine) and B12 (cyanocobalamin) have shown to be associated with exacerbation of acne vulgaris and outbreak of acneiform lesions^{4,7,10-12}.



Fig. 1. Diffuse centropacial erythema with evident erythematous papules.

Fig. 2. Regression of skin lesions after conducting topical therapy with metronidazole and cold compresses twice daily.



Rosacea fulminans has been reported following the administration of vitamin B derivatives, but in most cases the reactions were associated with excess recommended daily doses^{4,7}. Regarding therapy options, vitamin B-triggered rosacea, as well as other drug induced rosacea do not usually respond to standard rosacea treatments, but clinical symptoms tend to improve rapidly upon withdrawal of the incriminating agent^{7,10}. Our patient developed rosacea-like dermatitis after prolonged therapy with a fixed-dose combination of isoniazid (INH) 400 mg and pyridoxine (vitamin B6) 25 mg for current pulmonary tuberculosis. Pyridoxine, vitamin B6, is a hydrosoluble vitamin, which is important for proper functioning of the nervous system¹³. Isoniazid (INH) is a potent antimycobacterial agent, which is thought to act by inhibition of mycolic acids of *Mycobacterium tuberculosis*, thus inhibiting its cell wall synthesis¹⁴. It is an effective and widely used first-line antituberculous drug, but its use is related to the development of polyneuropathy, the well known toxicity associated with antituberculosis chemotherapy^{15,16}, appearing as tingling sensation and paresthesias¹⁵⁻¹⁷. Although the exact mechanism whereby pyridoxine deficiency causes polyneuropathy is still unclear, some researchers suggest that isoniazid forms a complex with pyridoxine, resulting in deficiency of biologically active pyridoxine^{15,16}. The risk of isoniazid induced polyneuropathy depends on the dose of isoniazid used, acetylator genotype, and associated risk factors such as older age, chronic alcoholism, diabetes, malnutrition, HIV-infection, pregnancy, lactation and usage of neurotoxic medication^{15,17}. Isoniazid induced polyneuropathy is preventable and easily treatable with pyridoxine, which acts preventively in low dosages and curatively in high dosages¹⁵. Therefore, pyridoxine is generally routinely prescribed and administered orally with isoniazid for tuberculosis patients in the industrialized world¹⁵⁻¹⁷. There is still tremendous variability in the recommendations regarding pyridoxine prophylaxis and therapy in the context of isoniazid treatment¹⁵. In our case, as the patient is a slow acetylator phenotype, she was on a lower dose of isoniazid and therefore also on a lower dose of pyridoxine, including 300 mg of isoniazid and 18.75 mg of pyridoxine every other day. Therefore, the daily recommended dosage was not exceeded but still induced rosacea-like dermatitis. We report this case

to draw attention to the rather rare skin side effect of vitamin B6 when used in dosages below the recommended daily dose, considering that this clinical presentation is usually associated with a dosage much higher than the suggested daily intake levels. This pyridoxine side effect, although relatively rare, is important to acknowledge, particularly in the areas with a high prevalence and incidence of tuberculosis, which may consequently result in a higher occurrence rate of this cutaneous adverse reaction.

Conclusion

The etiopathology of rosacea remains still unknown. Besides known triggering factors, one should be aware of drugs and vitamins as possible provoking factors for development of rosacea or worsening pre-existing condition. Therefore, we emphasize the importance of pyridoxine (vitamin B6) as a potential trigger factor for rosacea. Although this side effect of pyridoxine is relatively uncommon it is important to identify it as it can have large impact on patient quality of life as well as treatment compliance during anti-tuberculosis isoniazid therapy.

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Sažetak

ROSACEIFORMNI DERMATITIS UZROKOVAN PIRIDOKSINOM

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Rosacea je kronična upalna bolest kože nepoznate etiologije, obilježena remisijama i egzacerbacijama te kliničkom slikom centrofacijalnog eritema i pojavom teleangiektazija. Javlja se u odrasloj dobi, pretežito u 30-tim godinama, nešto češće u žena. Patofiziologija rosaceje još uvijek nije do kraja razjašnjena. Čimbenici rizika za pojavu bolesti su pozitivna obiteljska anamneza, svijetli fototip kože, izlaganje sunčevoj svjetlosti te konzumacija alkohola, kofeina, toplih napitaka i začinjene hrane. Međutim, neka istraživanja ukazuju na to da određeni lijekovi i vitamini također mogu biti provokirajući čimbenici u nastanku rosaceje ili pogoršanju već postojeće bolesti. Predstavljamo 53-godišnju bolesnicu u koje se razvio rosaceiformni dermatitis nakon započinjanja terapije fiksnom kombinacijom izoniazida i piridoksina (Eutizon®B6) i rifampicina (Rimactan®) u sklopu liječenja tuberkuloze.

Ključne riječi: *Piridoksin; Vitamin B6; Rozaceja – izazvana kemijskim supstancama*