OLGU SUNUMU CASE REPORT

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Cold Induced Neutrophilic Figurate Erythema

Soğukla İndüklenen Nötrofilik Figüre Eritem

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ABSTRACT We herein report a 35-year-old man presented with relapsing, rigorous, annular and archiform plaques with central clearing on the trunk, back, shoulders and forehead. They were remarkably aggravated after cold exposure. He had just begun taking anti-oxidant herbal pills containing *Ginkgo biloba* one month ago. On histologic examination, a perivascular inflammatory cell infiltrate composed of neutrophils and mononuclear inflammatory cells in the upper dermis wer seen. The unique features of this case were the relapsing and recalcitrant character of the lesions, the onset of the lesions after cold exposure and remission after warming or a rise in the body temperature. Though the presence of leukocytoclasia might have been a clue for vasculitis, the absence of other vasculitic histopathological findings such as nuclear dusts and negative direct immunofluorescence test have excluded vasculitis. We consider our case to represent a figurate erythema with a dominant infiltration of neutrophils that might be also induced by *Ginkgo biloba*.

Keywords: Erythema; ginkgo biloba; neutrophils

ÖZET Bu yazıda, gövde sırt, omuzlar ve alında merkezi iyileşme gösteren tekrarlayıcı, şiddetli, anüler ve kavisli plaklarla seyreden 35 yaşında erkek hasta sunulmaktadır. Lezyonlar dikkate değer bir şekilde soğuk maruziyeti sonrası alevlenmekteydi. Hasta 1 ay kadar öncesinde *Gingko biloba* içeren anti-oksidan bitkisel ilaçlar almaya başlamıştı. Histopatolojik incelemede, üst dermisde nötrofil ve mononükleer inflamatuar hücreleri içeren perivasküler inflamatuar hücre infiltrasyonu görüldü. Lezyonların tekrarlayıcı ve inatçı karakteri, lezyonların soğuk maruziyeti sonrası başlaması ve vücut ısısındaki bir artış ya da ısınma sonrası remisyona girmesi bu olguya özgü özellikler idi. Lökositoklazinin varlığı her ne kadar vaskülit için bir ipucu olabilirse de, nükleer artıklar gibi diğer vaskülitik histopatolojik bulguların yokluğu ve negatif direkt immünfloresan test vaskülit tanısını dışlamaktaydı. Biz bu olgunun *Gingko biloba* ile indüklenmiş olabilen nötrofil ağırlıklı infiltrasyona eşlik eden figüre eritemi temsil ettiğini düşünmekteyiz.

Anahtar Kelimeler: Eritem; *Gingko biloba*; nötrofiller

Figurate erythemas (FE) constitute a cluster of inflammatory cutaneous disorders, clinically characterized by annular, arcuate, serpiginous, or polycyclic lesions, widespreada or localized distribution, and transient or persistent behavior.[1,2] Neutrophilic figurate erythema (NFE) is a very rare inflammatory dermatosis, characterized by annular erythematous lesions, sometimes with polycyclic configuration[s] with histological feature of neutrophilic infiltration with nuclear dusts in the dermis.[1] Up to now, only three pediatric and three adult cases have been reported and none of the cases is known as drug induced.[1]

CASE REPORT

A 35-year-old man presented with intermittently relapsing, mildly pruritic, reddish, edematous swellings on his pre-sternal area, trunk, shoulders, and upper extremities which began first 8 months ago. He had no history of a suspicious contact, insect bite or a pet exposure. His medical history was unremarkable. He had a history of similar eruption over the same site a few months ago. He noted that the lesions were aggravated after cold exposure and interestingly resolved spontaneously after warming and a rise in body temperature such as hot bath, exercise or swearing. He also informed that he had just begun taking anti-oxidant herbal pills containing Ginkgo biloba on his own one month before the onset of the lesions. Though, the lesions were noted to be nearly stable for a few days till they improve after hot exposure. He refused consumption of moldy cheese. Systemic examination revealed no abnormalities.

Dermatological examination revealed firm, non-tender, erythematous, polimorphic plaques in annular and semi-annular or polycyclic configurations, measuring in 0.5-2 cm x 0.5-2 cm size on his chest, shoulders and back Figure 1 a, b. No trailing scale was noted. The centrifugal distribution of the annular plaques with central clearing was also remarkable.

Hemogram and biochemistry examinations including urinanalysis, erythrocyte sedimentation rate (ESR), transaminases, serum level of immunoglobulins G, M, and A, and, antistreptolysin O titer, rheumatoid factor, anti-nuclear antibodies, anti-ds-DNA autoantibodies, anti-SS-A (Ro), and anti-SS-B (La) antibodies were within normal limits. Anti- *Borrelia burgdorferi* IgG, anti-Epstein–Barr virus IgM and IgG, serum cryoglobulin tests and serum angiotensin converting enzyme levels were all negative. Chest X-ray, ultrasonography of the abdomen, and gastrointestinal endoscopy was noncontributory.

Informed consent has been obtained. Histopathological examination of the punch biopsy material taken from the border of the plaque lesion revealed a regular epidermis and perivascular and interstitial inflammation in the dermis (Figure 2-a). Perivascular and interstitial eosinophil, neutrophil and lymphocytic infiltration accompanying with swelling and proliferation of the endothelial cells were seen in the dermis (Figure 2-b). Though, nuclear dusts were not noted. Direct immunofluorescence (DIF) was negative. Patch test examination with *Ginkgo biloba* pills was negative.

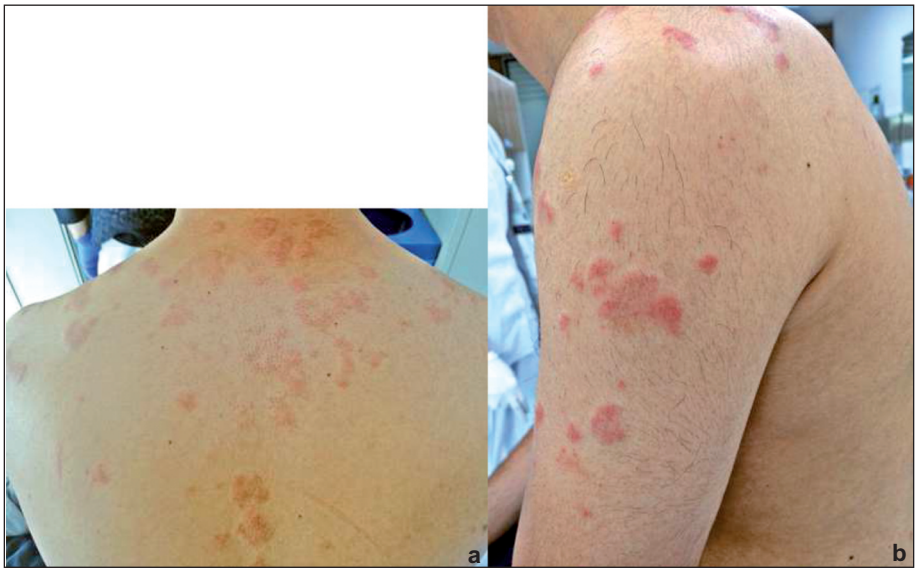

FIGURE1: a-b: Firm, non-tender, erythemathous, polimorphic plaques in annular and semi-annular or polycyclic configurations on his chest, shoulders and back.

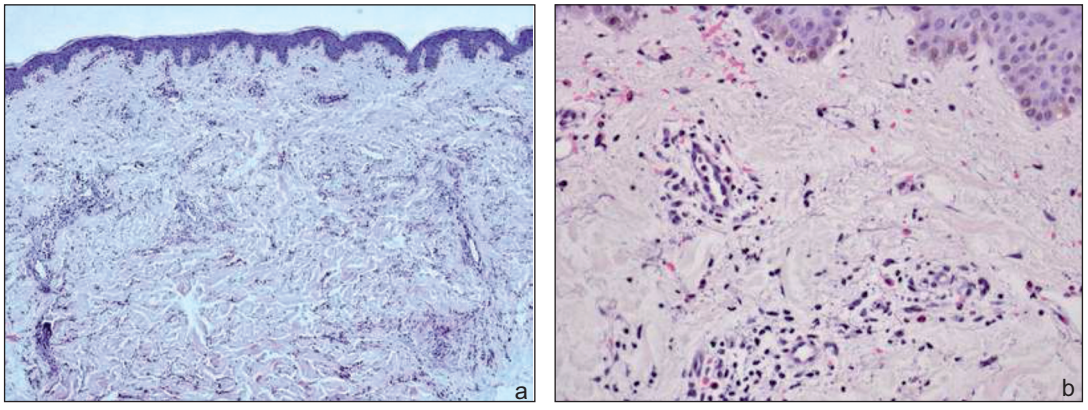

FIGURE 2: a: Epidermis is regular. Note the perivascular and interstitial inflammation in the dermis (HEx40); **b:** Perivascular and interstitial eosinophil, neutrophil and lymphocytic infiltration (HEx200).

Based on these clinical and histological findings, the patient was diagnosed with NFE. He stopped taking *Ginkgo biloba* pills and he was treated with colchicine tablet 1.5 mg/day and levocetirizine tablet 5 mg/day 3 months. The lesions almost completely improved. The patient was rechallenged with the same drug containing *Ginkgo biloba* for two weeks. This time, after 10th day of the drug administration the lesions reappeared on his back. In 1-year-follow up no flare up of the lesions was noted after the retreatment and discontinuation of the drug.

DISCUSSION

NFE is a rare inflammatory dermatosis, characterized by indurated, erythematous, polycyclic or annular lesions, with rapid centrifugal enlargement and histological feature of neutrophilic infiltration with nuclear dusts in the dermis.[1] NFE is characterized by a superficial and deep, perivascular and interstitial infiltrate of neutrophils associated with leukocytoclasis but without other signs of vasculitis.[1,2] It is characterized by papular erythematous eruptions with rapid centrifugal enlargement to annular or polycyclic asymptomatic plaques with indurated borders devoid of vesicles, crusts or desquamation.[1,2] Widespread or localized distribution, and transient or persistent behavior may all be seen in NFE.[2] The patches tend to disappear within 2-4 weeks, but the disease course is chronic. Relapses and recurrences are seen common.[2]

The differential diagnosis of NFE includes Sweet syndrome, plaque sarcoidosis, Jessner's lymphocytic infiltration, annular elastolytic giant cell granuloma, Sjögren's syndrome, neutrophilic type of urticaria, annular variant of subacute cutaneous lupus erythematosus (SCLE), causes of figurate erythema such as erythema chronicum migrans, erythema annulare centrifugum, erythema gyratum repens and its variant familial annular erythema.[1,3,4] Histopathological differential diagnosis of NFE consist some neutrophilic dermatosis such as rheumatoid neutrophilic dermatosis, Behcet's syndrome, urticarial vasculitis, bullous SLE, bullous variant of pyoderma gangrenosum and subcorneal pustular dermatosis.[2,5] Based on clinical, laboratory and histopathological findings, all these diseases could be eliminated. The indurated character and neutrophilic predominancy of the inflammatory infiltrate confirmed the diagnosis of NFE in our patient.

NFE belongs to those figurate erythemas of unknown etiology. As we know, only 4 adult cases of NFE have been reported in the literature.[1,6,7] In all of the previously reported cases of NFE, there was no history of insect bite or infection. The disease may be idiopathic in otherwise healthy individuals or present with some underlying diseases such as malignancies.[6] For instance, a 79-year-old female presented with indurated figurate lesions in upper and lower limbs including palms and soles had been diagnosed with NFE accompanying with cryptogenic hepatic cirrhosis and Hodgkin's lym-

phoma.[6] Moreover, another adult case of NFE presented with the morphology of erythema gyratum repens was also reported in a patient with systemic lupus erythematosus.[7]

Similar cold aggravation and presence of hot induced lesions were also remarkable in 1-year and 9-month-old white two boys with idiopathic NFE of infancy reported previously.[8] We believe that the diagnosis of cryoglobulinemia has to be excluded in the presence of this status. Complete resolution of the lesions were previously reported during febrile episodes in these cases and in a few cases with erythema annulare centrifigum (EAC).[8,9] After disregulation of some cytokine production in the skin triggered by cold, the skin lesions resolve with an increase in interferon if the body temperature rises to a degree higher than normal.[9] Moreover, NFE has been reported to show some clinical differences in paediatric cases such as benign, self-limiting course when compared with adult cases.[10] It usually resolves within a few months in infants. First of all some other diseases such as neonatal lupus erythematosus and its variant erythema gyratum atrophicans transiens neonatale, erythema chronicum migrans, erythema marginatum rheumaticum, EAC and its variant familial annular erythema, tinea corporis, linear IgA dermatosis, granuloma annulare, erythema multiforme, neonatal syphilis, annular erythematous lesions associated with Still's disease, and urticaria have to be excluded. Once a diagnosis of NFE of infancy is made, parents should be reassured, as this entity and its variants are unassociated with other conditions in most cases.[8,10]

Up to now drug induced NFE has not been reported before. In this report, we wanted to emphasize that our case is the first case of NFE which might have been induced by a herbal drug; *Ginkgo biloba* that has neuroprotective effects.[11] *Ginkgo biloba* has been demonstrated to cause suppression of nuclear factor kappa-B (NF-kB), and toll-like receptor 4 (TLR4)/NF-kB, the up-regulation of heme oxygenase 1, erythropoietin secretion and anti-apoptotic protein expression, the inhibition of pro-apoptotic proteins expression, and the improvement of endothelial nitric oxide (NO) synthesis.[11] Some of the latter molecular mechanisms such as the improvement of endothelial NO synthesis might have also act as a trigger for some of the histopathological findings such as swelling and proliferation of the endothelial cells and leucocytoclasia, seen in our case. The presence of perivascular and interstitial eosinophil infiltration in this case also confirms the drug-induced pathogenesis. Each capsule contains; 90 mg standardized *Gingko biloba* leaf extract (gingkoflavoglucoside) 21 mg 24%, terpene lactones 5 mg 6% and 45 mg elemental *Gingko biloba* leaf salt.[9] We experienced relapse of the lesions after rechallenge with the same herbal drug containing *Gingko biloba*. Moreover, the patch test results were negative. However, some other preser- vative substances or dyestuffs in the ingredients of the herbal drugs might have also caused this neutrophilic dermatosis; NFE in this patient. The good response of this case to colchicine was already expected as colchicine and dapson are well-known to be one the first choice treatments for neutrophilic dermatoses.[12] We think that some cases with NFE might have been possibly misdiagnosed or unreported. The reason of the relapsing course of NFE more or less at the same location is still not clear.

The exact pathological association of NFE with *Ginkgo biloba* and/or cold is not clear and further more clinical cases are needed to clarify the exact pathology of this disease. NFE should also be considered in differential diagnosis of the erythematous annular plaques in adults and detailed investigation of a probable malignancy, an underlying disease or a drug association and cold exposure must be performed. In recent years the use of supplemental medications; containing minerals, vitamins and anti-oxidant elements have increased worldwide without any prescription. We presented this case to focus on the importance of an accurate and detailed medication history and to remark a possible association of NFE and *Ginkgo biloba.*

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

All of the authors contributed to the concept of the article. When Pelin Üstüner received clinical data, he designed the article, analyzed it and contributed to his opinion. Pelin Üstüner also prepared the article. Pelin Üstüner and Ali Balevi, revised the article for intellectual content. Aslı Ünlü collects histopathological data and regulates pathological patterns. Mustafa Özdemir approved the final version.

REFERENCES

1. Ozdemir M, Engin B, Toy H, Demirkesen C. Neutrophilic figurate erythema. Int J Dermatol 2008;47(3):262-4.
2. Ríos-Martín JJ, Ferrándiz-Pulido L, Moreno-Ramírez D. [Approaches to the dermatopathologic diagnosis of figurate lesions]. Actas Dermosifiliogr 2011;102(5):316-24.
3. Naveen KN, Kalinga B, Pai VV, Athanikar SB, Sori T, Raju K, et al. Erythema gyratum repens like figurate erythema responding to topical steroid in a healthy individual. Indian J Dermatol 2013;58(4):329.
4. Baglieri F, Scuderi G. Erythema annulare centrifugum: a "deep type" figurate eruption. G Ital Dermatol Venereol 2012;147(1):129-31.
5. Nischal KC, Khopkar U. An approach to the diagnosis of neutrophilic dermatoses: a histopathological perspective. Indian J Dermatol Venereol Leprol 2007;73(4):222-30.
6. Trébol I, González-Pérez R, García-Rio I, Arregui MA, Saracibar N, Carnero L, et al. Paraneoplastic neutrophilic figurate erythema. Br J Dermatol 2007;156(2):396-8.
7. Khan Durani B, Andrassy K, Hartschuh W. Neutrophilic dermatosis with an erythema gyratum repens-like pattern in systemic lupus erythematosus. Acta Derm Venereol 2005;85(5):455-6.
8. Patrizi A, Savoia F, Varotti E, Gaspari V, Passarini B, Neri I. Neutrophilic figurate erythema of infancy. Pediatr Dermatol 2008;25(2):255-60.
9. Bottoni U, Innocenzi D, Bonaccorsi P, Carlesimo M, Faina P, Richetta A, et al. Erythema annulare centrifugum: report of a case with neonatal onset. J Eur Acad Dermatol Venereol 2002;16(5):500-3.
10. Maurelli M, Colato C, Tessari G, Girolomoni G. Neutrophilic figurate erythema: report of a new case in an adult and comparison between adult and paediatric cases. Eur J Dermatol 2016;26(6):634-5.
11. Nabavi SM, Habtemariam S, Daglia M, Braidy N, Loizzo MR, Tundis R, et al. Neuroprotective effects of ginkgolide B against ischemic stroke: a review of current literature. Curr Top Med Chem 2015;15(21):2222-32.
12. Konda C, Rao AG. Colchicine in dermatology. Indian J Dermatol Venereol Leprol 2010; 76(2):201-5.