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Acral erythema induced by interferon alpha in a child

İnterferon alfa tedavisi sırasında gelişen akral eritem

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SUMMARY: *A variety of side effects are associated with interferon alpha therapy during the treatment of chronic hepatitis B infection. In this paper, an 11-ys-old girl who developed acral erythema during interferon alpha therapy is described. This is the first reported case of acral erythema due to interferon alpha.*

Key words: Acral erythema, interferon alpha, chronic hepatitis B

ÖZET: *Kronik B hepatiti enfeksiyonu tedavisinde kullanılan interferon alfa'nın çeşitli yan etkileri vardır. Bu makalede, interferon alfa tedavisi sırasında akral eritem gelişen 11 yaşında bir kız hasta sunulmaktadır. Bu hasta interferon alfa tedavisine bağlı olarak gelişen ilk akral eritem olgusudur.*

Anahtar sözcükler: Akral eritem, interferon alfa, kronik B hepatiti

Recombinant interferon-α has been shown to be effective in the treatment of chronic viral hepatitis B in several studies (1-3). A variety of side effects have been described that may lead to a decrease in dosage, or discontinuation of therapy (4, 5). To the best of our knowledge, acral erythema has not been reported before among the side effects of interferon-α. We report a child who experienced this dermatologic side effect during α-interferon 2a therapy for chronic viral hepatitis B infection.

CASE REPORT

An 11 years-old-girl was referred to our department because of HBsAg positivity found during a routine check-up. Her medical history as well as family history was unremarkable.

Physical examination at admission was normal. Laboratory investigations including CBC, ESR, urine analysis, BUN, creatinine, calcium, phosphorus, alkaline phosphatase, total protein, albumine, total bilirubin, direct bilirubin, PT and PTT were within normal limits. ALT and AST were about four times the upper limit (ALT 136 U/L, AST 105 U/L). Serological analyses for HBV revealed that HBsAg and HBsAb was positive, HBeAg positive, HBeAb negative, Anti-HBc IgM negative and Anti-HBc IgG positive. Anti-delta and anti-HIV were negative. HBV DNA was found to be 152 pg/mL. Liver biopsy was consistent with chronic active hepatitis with a Knodell score of 8.

Interferon alpha 2a (Roferon®) was started with a dosage of 5 megaunits/m², twice weekly which was planned to be continued for six months. She was hospitalized for a week when the treatment was started, then observed as outpatient monthly. During the follow-up, physical examination was performed, CBC and biochemical analysis were repeated monthly and a blood sample for HBV serological analysis was taken at the third month of therapy.

When she was seen at the fifth month of therapy, she had complaints of dysesthesia on her hands followed by swelling, erythema, pain and tenderness which were present for about two weeks. Pain was partially limited the use of her hands, pruritus was absent. Physical examination revealed erythema and edema of the palms (Figure 1). At that time, CBC was normal, ESR 21 mm/h, AST 12 U/L, ALT 33 U/L; immunoglobulins, complements, ANA and anti-DNA levels were within normal limits. Acral erythema due to interferon-α was diagnosed based on these findings and interferon therapy was stopped. Her complaints and physical findings regressed and ceased by ten

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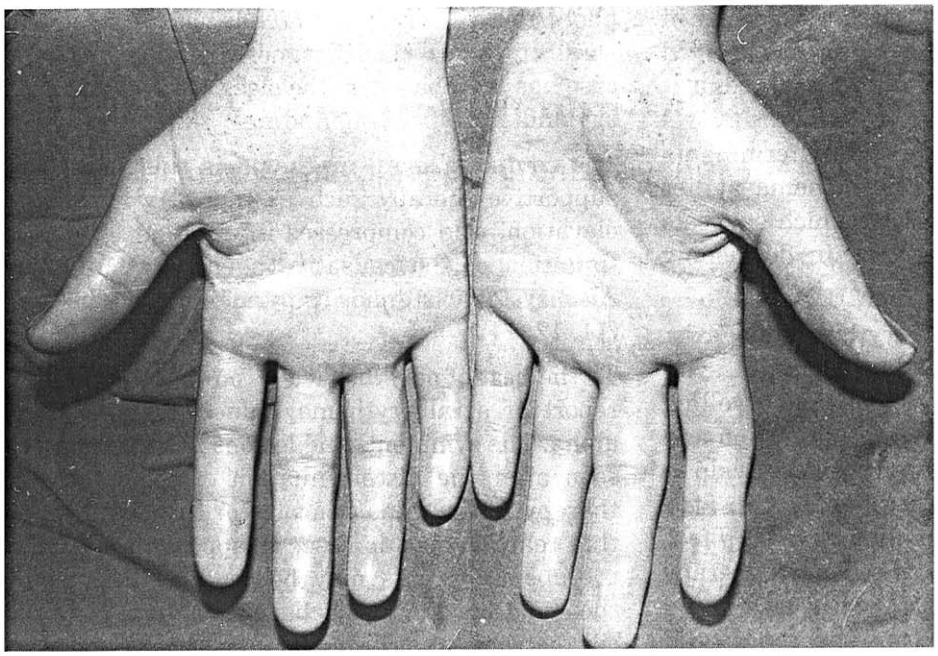

Figure 1. Erythema and edema of the palms

days. Serological analysis revealed a complete response to interferon therapy, that is, biochemical normalization, HBe antibody seroconversion as well as loss of HBV DNA. We have not restarted interferon alpha therapy and her symptoms did not recur during the follow-up.

DISCUSSION

The interferons are part of the host defense system against viral infections (6). Interferons are composed of three classes, namely alpha, beta and gamma interferons. Interferon alpha is produced in response to viral infection and other antigenic stimulation. It has also antineoplastic as well as immunomodulatory effects.

Recombinant interferon alpha 2a has been shown to be effective in the treatment of chronic viral hepatitis B (1). It has also become available for the treatment of chronic active hepatitis in children (2, 3).

The side effects of alpha interferon can be a major impediment to its use. High doses, formerly used in cancer patients, were associated with severe side effects. As experience with the use of alpha interferon has grown, dosages have been lowered and toxicity has decreased but remains a problem. At lower dosages, side effects are less frequent and less severe and may be difficult to recognise. In most trials, 5 or 10 megaunits was given 3 times weekly for 3, 4 or 6 months. The twice weekly dosing schedule was generally associated with fewer side effects and similar response rates with daily administration (1-3, 7). Our dosing schedule for chronic hepatitis B is 5 megaunits/m^2 twice weekly for 6 months which we instituted to the presented case.

Variety of side effects of interferon alpha have been described including flu-like syndrome, infections, hematologic, autoimmune, neuropsychiatric and systemic effects. It may also lead to various cutaneous complications including elongation of the cilia, alopecia, reactivation of herpes labialis and radiation recall phenomena (8). Exacerbation of chronic dermatologic conditions, such as psoriasis (9) and lichen planus (10) have also been reported. Acral erythema as a side effect of interferon alpha has not been reported before.

Acral erythema is a rare cutaneous complication of different chemotherapeutic agents which may be observed with fluorouracil, doxorubucin and especially cytosine arabinoside treatment. Infrequently, it has been reported with hydroxyurea, methotrexate, mercaptopurine, cyclophosphamide and mitotane (11).

The etiology of acral erythema is unknown but temperature gradient, vascular anatomy, the high concentration of ecrin glands and rapidly dividing epidermis are thought to play role in the etiology.

It is mostly seen in adults although it can occur in children (11, 12). Acral erythema can be observed from 24 hours to 10 months of the therapy but it seems to be dose-dependent. Both peak drug level and total cumulative dose are the determinants (11). Our case developed acral erythema at her fifth month of interferon therapy which suggests that cumulative dose played role in developing this condition.

Several clinical types of acral erythema may exist including a prodrome of dysesthesia, painful, symmetric, well-demarcated erythema and swelling on the palms and soles, blistering, ulceration and rarely erythema on the trunk, neck, chest, scalp or extremities (11, 13). The healing occurs with hyperpigmentation, desquamation and reepitelization in one or two weeks after the chemotherapy is ceased. The diagnosis is generally evident on the basis of this clinical setting and course (11, 12). In the histopathologic examination, there is mild spongiosis, vacuolar degeneration of the basal cell layer, necrotic and dyskeratotic keratinocytes, papillar edema and perivascular lymphohistiocytic infiltrate which is not diagnostic for acral erythema (11). Diagnosis of the presented case has been based on the classical symptomatology and accompanying findings.

The course of acral erythema is self-limited; so supportive therapy such as topical wound care, elevation, cold compresses in addition to discontinuation of the causative agent are sufficient. Also, systemic steroids or pyridoxine may be used (11, 12, 14).

To the best of our knowledge, our case is the first report of acral erythema induced by interferon alpha. The symptoms and lesions had disappeared soon after the discontinuation of the interferon therapy. There is no other factor that can explain this reaction in our case. It appears that many therapeutic agents may be capable of inducing this syndrome and we believe that there is a relation between interferon alpha treatment and acral erythema. Although self-limited and without any important consequences, this clinical condition must be kept in mind during interferon alpha therapy.

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