Facial hyperpigmentation during pegylated interferon alpha therapy for chronic hepatitis B infection

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To the Editor,

Adverse skin reactions with the use of interferon (IFN) alpha alone or in combination with ribavirin have been described in previous reports (1). Hyperpigmentation associated with both standard and also pegylated IFN alpha has also been reported in recent years (2-7). However, all patients had chronic hepatitis C, hyperpigmentation being mostly at tongue and injection sites, and they were on a combination treatment with ribavirin in these reports. In this article, we present, to our knowledge, the first case of facial hyperpigmentation during pegylated IFN alpha therapy in a patient with chronic hepatitis B infection.

A 52-year-old male patient was admitted to our clinic for HBsAg positivity. HBV-DNA viral load was 3.4 million IU/mL. A liver biopsy revealed chronic hepatitis B with moderate inflammation and stage II fibrosis (Ishak). A treatment with pegylated IFN alpha-2a 180 μg weekly was started. At 12 weeks of therapy, significant hyperpigmentation evolved in his temple, nose, cheeks and jaw (Fig. 1). Laboratory tests including complete blood count, routine biochemistry, thyroid functions, the level of ferritine, ACTH and cortisol were in normal range. A skin biopsy from affected areas revealed increased melanin pigment in the basal layer of the epidermis and solar elastosis and melanophages in the dermis. Masson-Fontana staining highlighted deposition of melanin in the basal layer and adjacent areas. Complete virologic and biochemical response was achieved at 12 weeks of therapy. IFN was continued with the patient's consent and completed to 48 weeks. At the end of the treatment hyperpigmentation was persisting, however, in the first year after treatment it regressed significantly without complete resolution.

Hyperpigmentation is a well-known cutaneous side effect of various drugs (8). Hyperpigmentation secondary to standard or pegylated IFN has been reported in a total of 12 cases with chronic hepatitis C infection in previous publications (2-7). The lesion was described at the tongue and/or injection site in all these patients. Although the role of IFN was stressed more significantly in these reports, a contributing role of ribavirin could not be totally excluded. Hyperpigmentation has not been reported before in a patient with hepatitis B or any patient using IFN alone. Therefore, our case has three distinctive contributions to the literature ; 1) it is the first case of hyperpigmentation in a hepatitis B patient related to IFN, 2) the first time hyperpigmentation has been shown associated with IFN alone, and 3) hyperpigmentation was located at the facial area rather than tongue or injection sites.

Fig. 1. — Prominent hyperpigmentation on the patient's temple, nose and periorbital region.

The mechanism of hyperpigmentation secondary to IFN is not clear yet, however, an IFN-mediated up-regulation of melanocyte stimulating hormone (MSH) receptors and increased secretion of MSH have been postulated in previous studies (2,7). In a murine model, IFN has been shown stimulate differentiation of melanocytes by increasing the expression of surface MSH receptors and increase pigment production (9). Authors suggest that such a mechanism may in part be responsible for post-inflammatory and drug induced skin pigmentation, and provides an additional basis for action in the clinical responses of melanoma to IFN treatment. Skin biopsy of our patient shows clearly the accumulation of melanin in the basal layer of hyperkeratotic epidermis and suggests an increase in pigment secretion probably induced by IFN.

All cases of hyperpigmentation related to IFN have been reported during the course of hepatitis C in previ-

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ous reports (2-7). It is also not clear if ribavirin has an additional role for development of hyperpigmentation in these patients. Photoallergic skin reaction in a patient with hepatitis C has been attributed to ribavirin in a case report (10). However, the data in these reports are inconclusive as ribavirin and IFN were given together in hepatitis C patients. It is also not clear why hyperpigmentation develops in a very small group of patient using IFN therapy.

The lesions usually regressed or improved after the end of the treatment in previous reports, thus, the discontinuation of therapy is not recommended. The data about full recovery of lesions are not clear in the literature and long-term follow-up probably is needed.

This case more clearly demonstrates the association of IFN with hyperpigmentation and shows that it can be seen at different part of the skin. Clinicians should be aware of such an adverse effect of IFN treatment and counsel the patients in such case.

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