Severe Raynaud syndrome induced by adjuvant interferon alfa in metastatic melanoma

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ABSTRACT

Melanoma is the most lethal form of skin malignancy because of its aggressive behaviour. In advanced disease, interferon alfa can be used as adjuvant therapy. However, this therapy is not free of side effects. We present a case of severe Raynaud syndrome and digital necrosis induced by interferon alfa in a patient with melanoma. Pathogenic mechanisms are discussed.

KEY WORDS

Melanoma, treatment, interferon, adjuvant, Raynaud syndrome, digital necrosis, vascular toxicity

1. INTRODUCTION

Interferon alfa is a biologic response modifier and the best agent for adjuvant treatment of patients with melanoma in stages II and III, improving relapse-free and overall survival [1]. Its immunomodulating, anti-proliferative, and antiviral properties have also proved therapeutic for viral hepatitis, hematologic malignancies, and solid and vascular tumours. The most common side effects are fever and flu-like symptoms, myalgia, fatigue, cephalea, weight loss, and depression [2]. Other effects, such as cardiovascular effects (myocardial infarction, arrhythmias, cardiomyopathy), are less common [2].

Raynaud syndrome is rare, and the severe type, leading to digital ischemia and necrosis, is exceptional. In this report, we highlight a potential serious toxicity of interferon alfa in a patient with melanoma whose treatment with that agent had to be discontinued because of severe Raynaud syndrome and eventual digital necrosis.

2. CASE REPORT

A 47-year-old woman underwent surgery for ulcerated nodular melanoma with a Breslow thickness of 5 mm and level IV infiltration. Surgical margins were free of disease. Positron-emission tomography was performed to stage the melanoma, and imaging showed captation in pelvic lymph nodes. After lymphadenectomy, histology confirmed metastatic melanoma, and subsequently, adjuvant therapy with interferon alfa at a dose of 10 MU/m^2 3 times weekly was started.

Five months later, the patient attended our hospital emergency department reporting painful and cyanotic digits 2 and 3 of the left hand. In her history, the patient reported Raynaud syndrome of several years' duration, which worsened in the preceding 3 months, with skin changes in the hand within the preceding 12 moths and pyrosis with regurgitations.

Physical examination showed telangiectasia in face and neck, acrosclerosis, and digital necrosis in fingers 2 and 3 of the left hand (Figure 1). Avascular areas and splinter hemorrhages were observed in capillaroscopy. Barium swallow showed gastroesophageal reflux and severe esophageal hypomotility. Antinuclear antibody with nucleolar form and anti–Scl-70 were positive.

Interferon alfa had to be discontinued, and intravenous prostaglandin infusion was initiated. After 1 week, the necrosis disappeared, and the patient's skin recovered completely. Unfortunately, our patient died a few weeks later with disseminated disease.



FIGURE 1 Digital necrosis induced by interferon alfa, involving fingers 2 and 3 of the left hand.

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3. DISCUSSION

The existing Raynaud syndrome in our patient, who showed criteria for scleroderma (telangiectasia, Raynaud syndrome, acrosclerosis, regurgitations, pathologic capillaroscopy, and anti–Scl-70 antibodies) and who had not been diagnosed, was probably aggravated by interferon alfa, leading to digital necrosis.

Interferon alfa is the only adjuvant therapy for melanoma that has been shown to have a reproducible benefit. Three cooperative group studies showed improvement in relapse-free survival, and two of the three also showed significantly improved overall survival among patients receiving high-dose interferon alfa [3–5].The U.S. Food and Drug Administration approved this treatment for patients with primary melanoma lesions thicker than 4 mm (stage IIB or IIC) or disease involving regional lymph nodes (stage III). The exact role of interferon alfa has yet to be defined: it has been proposed that the benefit of interferon alfa is proportional to the risk of recurrence and that this therapy can be considered for all patients in whom the potential benefit outweighs the expected toxic effects.

The association of Raynaud syndrome with interferon alfa is rare. Although the median time from start of treatment to development of symptoms is 18 months [6], symptom development in the first months, as in our patient's case, is not unusual. Often symptoms and signs are limited to between 1 and 3 digits, but in more severe cases, hands and feet alike are affected, leading to frank necrosis of digits. It has been suggested that, by more scrupulously talking with patients, a higher incidence of interferon-induced vascular complications can be found [6].

The implications, for treatment policy, of the development of Raynaud syndrome and digital necrosis with interferon alfa remain unclear. In patients with mild attacks, therapy has been continued without aggravation of symptoms. In more severe cases, as with our patient, interferon alfa is discontinued, and treatment with calcium antagonists or prostaglandins is initiated [7–10]. Anticoagulants have also been used [11]. Symptoms improve in most cases; however, it remains unclear whether the improvement is related to discontinuation of interferon alfa or to induction of vasodilators. Sometimes, ischemia progresses despite the use of vasodilators, and amputation of digits is needed [7].

4. CONCLUSIONS

As indicated in the work published by Hauschild [12] in the May issue of *Current Oncology,* we strongly think interferon alfa definitely has value for patients with high-risk cutaneous melanoma. However, dermatologists and oncologists should be aware that interferon alfa may cause peripheral vascular toxicity and substantially reduce overall quality of life in these patients.

Clinical suspicion and recognition of the connection between symptoms and pharmaceuticals are of utmost importance. In severe cases, to avoid digital necrosis, interferon alfa must be discontinued, and intravenous prostaglandins started.

5. REFERENCES

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