Medical Oncology (2000) 17, 64–69
 1357-0560/00 $15.00
www.nature.com/mo

CASE REPORT

Dermatomyositis after interferon alpha treatment

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An association between auto-immune disorders and interferon (IFN) has been reported. High levels of natural IFNα are present in the blood of patients with auto-immune disease and correlate with disease activity. In addition, IFNα treatment of humans has resulted in multiple reports of associated auto-immune phenomena. We describe a patient who underwent resection of regionally metastatic melanoma, was given adjuvant high-dose IFNα2b, and subsequently developed dermatomyositis. To the authors' knowledge this is the first report of dermatomyositis in association with IFNα treatment. We review the literature reporting associations between IFNα and auto-immune disease and discuss possible mechanisms by which IFNα may contribute to the development of auto-immune disease. High dose IFNα2b is more commonly prescribed since it was approved as an adjuvant treatment for patients with surgically resected high-risk melanoma. The potential for cases of IFN-associated auto-immune disease is therefore a clinical concern. Standard side effects of high-dose IFN therapy resemble symptoms of auto-immune diseases, which may make prompt diagnosis difficult. Therefore, it is important that auto-immune diseases such as dermatomyositis are recognized as potential side effects of treatment with high-dose IFNα.
Medical Oncology (2000) **17**, 64–69

Keywords: interferon-alpha; treatment complications; auto-immune disease; dermatomyositis; neoplasms; melanoma

Case Report

PB was healthy until March 1995 when at the age of 57 she was diagnosed with a Breslow depth 1.05 mm, Clark's level IV, malignant melanoma on her right knee. Wide local excision was then performed and the pathologic evaluation revealed no residual tumor and clear margins of 1.5–2 cm. Evaluation including chest X-ray, complete blood count and liver chemistries revealed no evidence of metastatic disease. She was followed clinically without recurrence of disease until presenting with a palpable right inguinal node in July 1996. Excisional biopsy of this lymph node revealed involvement of this node with malignant melanoma. Work-up at that time included CT scans of the head, chest, abdomen and pelvis and revealed no evidence for additional disease. Adjuvant high-dose interferon alpha (IFNα) 2b (Schering Corporation, Kenilworth, New Jersey, USA) was started on 3 September 1996. She received 33 million units (20 million units/m^2) intravenously, 5 days per week for 4 weeks. After this induction treatment, the IFN dose was changed to 16

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Received 10 July 1999; accepted 19 July 1999

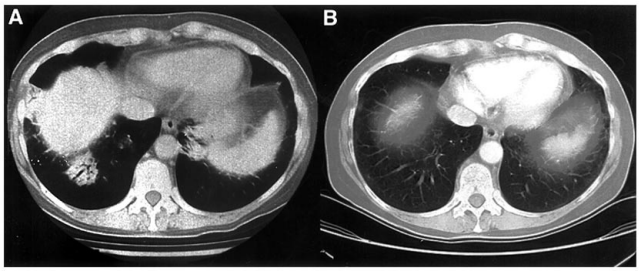

Figure 1 *(a) Interstitial pulmonary infiltrates at time of dermatomyositis diagnosis. (b) Resolution of pulmonary infiltrates after discontinuation of IFN and treatment with methotrexate and prednisone.*

million units (10 million units/m^2) by subcutaneous injection three times per week beginning 2 October 1996. During the induction therapy the patient reported fatigue but no nausea, vomiting, fever, chills, sweats or myalgia. Two and a half weeks after the subcutaneous IFN was initiated (six and a half weeks after high-dose IFN was started), she complained of swelling and stiffness in her hands, severe fatigue, myalgia, arthralgia and weakness. The IFN was discontinued and low dose dexamethasone was initiated at 1 mg twice daily. On 29 October she was noted to have rales on physical examination and chest CT scan showed bilateral lower lobe interstitial infiltrates consistent with inflammation (Figure 1a). Rheumatologic examination on 15 November found synovial thickening, warmth and tenderness of bilateral wrists, 2nd and 3rd metacarpophalangeal, and 2nd and 3rd proximal interphalangeal joints. The patient also had tenderness of her trapezius, deltoid, biceps, quadriceps and gluteal muscles as well as diminished strength with upper extremity abduction and flexion at the shoulders. A violet discoloration and edema of her eyelids were present. Laboratory evaluation revealed: Westergren erythrocyte sedimentation rate 43 mm/h (normal 0–30), creatine kinase 700 U/L (normal 21–183), aldolase 25.4 U/L (normal 1.2–7.6) and anti-Jo 1 antibodies markedly positive at 407.5 U (normal 0–26) by enzyme immunoassay. The presence of anti-Jo 1 antibodies was confirmed by immunoblotting against whole cell MoLT extract. Thyroid panel was normal. Rheumatoid factor, ANA, anti-ds DNA, anti-Smith, antihistone, anti-Ro, anti-La and RNP antibodies were negative. Complement levels were normal. Muscle biopsy obtained 12 December, 1996 revealed scattered necrotic fibers and basophilic, regenerative fibers consistent with an inflammatory process. At the time of the biopsy, the serum aldolase had decreased to 13 U/L. She was referred to the University of Wisconsin Hospital and Clinics at this time, weekly methotrexate at a dose of 12.5 mg was prescribed, and the dexamethasone was tapered. Her rheumatic symptoms improved until October 1997, when she had an exacerbation of myalgia and weakness which necessitated the addition of prednisone 10 mg per day to her regimen. The pulmonary infiltrates gradually improved and had entirely resolved by the December 1998 CT scan (Figure 1b). When seen in December 1998, her pain was improved and the prednisone had been tapered to 4 mg/d. She has had no evidence of recurrence of malignant melanoma more than $2\frac{1}{2}$ years after surgical resection of her regionally metastatic malignant melanoma. A repeat anti-Jo1 antibody performed in December 1998 was positive at a low level of 50 U (normal 0–26).

Discussion

Dermatomyositis

We describe a patient with American Joint Committee on Cancer (AJCC) Stage III melanoma who was treated with resection and adjuvant high dose IFNα 2b and subsequently developed anti-Jo 1 antibody-associated dermatomyositis (DM) with interstitial lung disease and arthritis. Dermatomyositis is an inflammatory myopathy characterized by skin rash and proximal muscle weakness. Common skin manifestations include lilac discoloration of the eyelids with periorbital edema (heliotrope rash) as well as raised, scaling, violaceous patches on the knuckles (Gottron's patches/papules), and erythema of the face, neck and upper torso. Dilated capillary loops in the nail folds and dry, fissured, scaling hands (mechanic's hands) may also develop. The muscle weakness is generally symmetric involving proximal limb muscles, neck flexors, pharyngeal muscles and, in severe cases, respiratory muscles. Muscle symptoms may occur after the dermatologic findings develop or concurrently with the skin manifestations. Dermatomyositis was once thought to be 'Polymyositis with a rash' but pathologic and immunologic differences have distinguished these two entities, as well as the related diagnosis of inclusion body myositis, as three distinct subcategories of inflammatory myopathy.[1] Pathologic features of the involved muscles in dermatomyositis include inflammatory infil-

trates in perivascular or interfascicular areas, microinfarcts with necrotic and regenerating fibers, and perifascicular atrophy of muscle fibers.[2,3] Intramuscular blood vessels show hyperplasia, thrombi within the vessels, and obliteration of capillaries. The cells that make up the inflammatory infiltrates consist primarily of B cells, a high CD4 to CD8 ratio among T cells, and CD4 cells in close physical proximity to B cells and macrophages. There is a relative paucity of lymphocytes infiltrating non-necrotic muscle fibers,[2,4–6] These features reflect the immune mechanism, which is thought to be primarily humoral and directed against the microvasculature.[7] In contrast, polymyositis (PM) and inclusion body myositis (IBM) are characterized by antigen-directed, T cell mediated attack on muscle fibers that express major histocompatibility (MHC) Class I antigen. Pathologic specimens in PM and IBM demonstrate inflammatory infiltrates in the fascicles which are predominately CD8 positive lymphocytes and macrophages. These cells surround and destroy non-necrotic muscle fibers.[5,8–10] Many patients with inflammatory myopathy have serum antibodies against nuclear or cytoplasmic antigens.[11,12] These antibodies are associated with connective tissue disease in general and therefore are not specific for myositis. Recently, however, myositis specific auto-antibodies have been described.[13–16] The most frequent of the myositis specific auto-antibodies is anti-Jo 1 which is directed against histidyl-tRNA synthetase.[15] Anti-Jo 1 antibody is associated with interstitial lung disease, non-erosive arthritis and Raynaud's syndrome and portends a poor prognosis.[17–19] Our patient had clinical features, pathology, and auto–antibodies that clearly define a diagnosis of dermatomyositis. MEDLINE search of the world literature from 1965 to the present resulted in no cases of dermatomyositis associated with IFN treatment. We report the first case, to the best of our knowledge, of dermatomyositis in association with IFNα treatment.

Dermatomyositis and malignancy

Dermatomyositis is associated with cancer in 6–45% of adult cases and many cases of cancer-related dermatomyositis appear to be paraneoplastic rather than coincidental.[20–23] When defined as paraneoplastic, there is a temporal relationship between the diagnosis of cancer and the onset of DM. In addition, the course of the inflammatory myopathy parallels that of the malignancy.[24,25] In fact, one extensive review of the literature notes that the diagnosis of cancer or recurrent cancer is usually made within 1 year of the myositis diagnosis.[26] Only ten cases of dermatomyositis associated with melanoma are reported in the literature.[26–30] In our case, the DM developed after the tumor was completely resected and was temporally related to the administered interferon therapy. To date there has been no evidence of recurrence of melanoma over the $2\frac{1}{2}$ years since her surgery for regionally recurrent disease. Therefore, the likelihood that her diagnosis of DM represents a paraneoplastic process is low.

Interferon and auto-immune disease

The administration of adjuvant therapy with high-dose IFNα was temporally related to the development of an inflammatory myopathy and suggests IFNα as a possible trigger of our patient's disease process. Interferons were originally described as soluble anti-viral glycoproteins.[31] They are now known to be a family of proteins secreted from cells in response to various stimuli such as viral infection, double-stranded RNA, antigens and other low molecular weight agents.[32,33] There are three major classes of IFN: IFN alpha is produced by leukocytes, IFN beta is produced by fibroblasts, and IFN gamma is produced by T-lymphocytes. Our patient was treated with recombinant IFNα 2b (Schering Corporation, Kenilworth, New Jersey, USA), which is a subclass of the alpha interferons.

The effects of IFNα include anti-proliferative effects, modulation of cell differentiation, increased cell surface expression of MHC Class I and Class II antigens, increased expression of Fc receptors on T cells, and increased cytotoxic activity of natural killer cells, lymphocytes and macrophages.[33–39] IFNα has also been shown to modulate the expression of more than 40 genes through activation at the transcriptional level.[40] The above-mentioned immunoregulatory properties suggest development of an auto-immune or inflammatory disease may be a potential side effect of IFN therapy. In fact, the association of auto-immunity and IFN treatment has been reported. Animal models show that lupus-prone mice treated with IFN alpha and gamma develop more rapid progression of disease and have shorter survival than those not treated with IFN.[41] Normal newborn mice treated with IFN develop immune complex nephritis.[42] One study using pokeweed-mitogen stimulated lymphocytes found that

IFNα induced *in vitro* production of antibodies with a lupus-associated idiotype.[43] IFNα treatment of humans with viral hepatitis and malignancy has resulted in multiple reports of associated auto-antibodies and auto-immune conditions such as immune cytopenias, pernicious anemia, thyroid dysfunction, systemic lupus erythematosus, rheumatoid arthritis, leukocytoclastic and digital vasculitis, and nephritis.[39,44–51] In these reports, nonspecific auto-antibodies were quite common; however, specific auto-antibodies or high titers of auto-antibodies with associated symptoms were much less frequently noted.

Another association between auto-immune disease and IFN is the presence of high levels of natural IFN in the blood of patients with auto-immune disease. Serum IFN detected in patients with various auto-immune diseases was originally thought to be gamma interferon based on inactivation at pH 2, but was more recently characterized as a type of IFNα.[52,53] A more recent study found elevated IFN levels in 70% of patients with SLE and confirmed that the IFN present was IFNα.[54] It has been stated that when more sensitive methods are used, more than 90% of patients with SLE have circulating IFN.[55] A correlation of disease activity and elevated IFN levels appears to exist as patients with active disease are more likely to have an elevated IFN level than those with quiescent disease.[52,54,56,57] In addition, IFN titers within the same patient usually correlate with disease activity.[54,58]

Although an association between IFN and auto-immune diseases has been reported, the exact relationship remains unclear. Production of pathogenic antibodies is a potential mechanism by which IFN may contribute to the development of auto-immune disease. Many patients treated with IFN have been found to have nonspecific auto-antibodies, but the development of clinical disease is much less frequent. In addition, patients with auto-antibodies prior to treatment are more likely to develop auto-immune disease.[39,46] Therefore, an underlying predisposition may be necessary in order for clinically overt disease to develop. This theory is supported by animal models and *in vitro* data.[41–43] IFN is known to increase cytotoxic activity of lymphocytes, macrophages and natural killer cells, increase Fc receptor expression, and increase expression of Class I and II MHC antigens.[33–38] This could result in increased B lymphocyte function and increased presentation of self-antigens. These actions correlate with the proposed immune mechanisms of damage in PM and DM as well as for other auto-immune diseases. IFN has also been shown to increase transcription of many genes including some with immune regulatory products. This is another potential mechanism for the development of auto-immunity.

Conclusion

High dose IFNα 2b is approved by the Food and Drug Administration as adjuvant therapy for patients with surgically resected Stage IIB and III melanoma.[59] Consequently, high dose IFNα 2b is being used with much greater frequency. The usual toxicities of IFNα are dose related and include fatigue, anorexia, fever, chills, myalgias, headaches, weight loss, myelosuppression, hepatic toxicity, and GI disturbances. The potential for cases of IFN associated auto-immune disease with higher dose IFN therapy is a clinical concern. The spectrum of toxicities frequently seen with high dose IFN therapy also resembles many of the symptoms of auto-immune disease, which may make prompt diagnosis difficult. For these reasons, it is important that physicians are aware that auto-immune diseases such as DM are a potential side effect of treatment with high-dose IFNα 2b.

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