A Case of Fatal Pemphigus vulgaris in Association With Beta Interferon and Interleukin-2 Therapy

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Beta interferon (β-IFN) and interleukin-2 (IL-2) have been utilized in experimental cancer therapy because of their effects on the immune system. We report here a patient treated with IL-2 and β-IFN who rapidly developed an immune-mediated, bullous exfoliative dermatitis and who ultimately died. Various etiologic mechanisms are proposed.


Beta interferon (β-IFN) and interleukin-2 (IL-2) have been utilized in experimental cancer therapy because of their effects on the immune system. Therefore, toxicities relating to disturbances of immune function are not unexpected.

We report here a patient treated with IL-2 and β-IFN who rapidly developed an immune-mediated, bullous exfoliative dermatitis and who ultimately died.

Case Report

An otherwise healthy 48-year-old man had developed inguinal adenopathy in 1984. Biopsy revealed a nodular poorly differentiated lymphocytic lymphoma. Staging revealed retroperitoneal adenopathy, splenomegaly, and bone marrow involvement. He was treated with Cytoxan (cyclophosphamide), vincristine, and prednisone for 11 months. Progression was noted in November 1985 and he was treated with radiotherapy to cervical, inguinal, paraaortic, pelvic and mantle fields at various times between December 1985 and February 1987 for local palliation. In March of 1987 he received trimetrexate without benefit.

Because of progressive, diffuse lymphadenopathy and an enlarging retroperitoneal mass, he was entered on CALGB study 8653 and he received β-IFN $5 \times 10^6$ U/M² and IL-2 $5 \times 10^6$ U/m² intravenously (IV) for one dose; two doses were given on days 2 and 4 at a 50% dose reduction because of fever and hypotension. On days 5 and 6 he noted small vesicles on his hands and torso which rapidly enlarged and spread to involve large areas of his skin (Figs. 1 and 2). A Tzanck preparation was negative. A punch biopsy of the skin demonstrated suprabasilar bullous formation and was believed to be most consistent with a diagnosis of Pemphigus vulgaris. Direct immunofluorescence on fixed tissue was nondiagnostic due to high background staining, but indirect immunofluorescence (Mayo Labs, Rochester, MN) of the patient’s serum was positive against an intercellular epidermal antigen. Despite therapy with high-dose corticosteroids his skin lesions progressed and new vesicles continued to form. Repeated episodes of sepsis from cutaneous sources were aggressively treated but ultimately led to his death after a 5-week hospitalization.

Discussion

This patient’s treatment with β-IFN and IL-2 was temporally related to the development of a severe dermatologic toxicity and death, and these drugs must be suspected to be causal.

P. vulgaris is an autoimmune skin disease with an incidence of less than one per 100,000 in the United States. A high proportion of patients have antibodies directed against the skin. Neither pemphigus nor the related disease pemphigoid are strongly associated with non-Hodgkin’s lymphoma, although there have been scattered case reports linking the two diseases. Pemphigus has been associated with autoimmune diseases (systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, and pernicious anemia), some drugs, hyposensitization injections for allergy, and thymoma.

A computerized literature search relating pemphigus to IL-2 or interferon for the years 1984 to 1987 revealed three citations. These investigators reported consis-
molytic anemia, as well as cutaneous vasculitis, nephrotic syndrome, maculopapular skin eruptions, and interstitial nephritis.\textsuperscript{14-20}

Interleukin-2 regularly causes hypotension, chills, and fever at the doses used in this study. Life-threatening toxicities associated with high-dose therapy (myocardial infarction, respiratory failure, gross edema) have not been seen at these doses\textsuperscript{21,22}. Dermatologic and immune toxicities have been noted for these drugs. Interleukin-2 alone has been associated with development of a Coombs positive hemolytic anemia, eosinophilia, and exacerbations of polymyositis/dermatomyositis.\textsuperscript{21} Therapy with IL-2 has been associated with the development of macular and diffuse erythoderma with pruritis and burning which resolves with desquamation after cessation of IL-2.\textsuperscript{23} Erythema nodosum has also been noted with IL-2.\textsuperscript{24}

Interleukin-2 and $\beta$-IFN have also been extensively studied \textit{in vitro} and in animal models. Both have been demonstrated to directly affect B-cell growth and immunoglobulin production.\textsuperscript{25-27} Alpha interferon is also capable of accelerating autoimmune disease in animals.\textsuperscript{28,29} It is possible that these actions of IL-2 and $\beta$-IFN led to the \textit{in vivo} appearance of an autoantibody to skin in the patient described herein. It is interesting to

tently low levels of IL-2 production and IL-2 receptor expression in phytohemagglutinin (PHA)-stimulated lymphocytes from patients with pemphigus. These levels returned to normal with successful treatment. Whether these abnormalities are pathogenic or reactive is unknown, but they suggest that IL-2 plays a role in the disease.

Beta interferon has had no direct dermal toxicity in animal tests. In human studies $\beta$-IFN has been exceedingly well tolerated as a single agent at doses ranging up to 500 $\times$ 10$^6$ U/m$^2$. Flu-like symptoms are common. Dermatologic toxicities have not been noted.\textsuperscript{13} Beta interferon administration to patients has not been associated with autoimmune phenomena, however the experience with $\beta$-IFN is comparatively small. Alpha interferon (alpha-IFN), which is functionally similar to and shares a receptor with $\beta$-IFN, has been used much more widely and has been associated with the development of several autoimmune diseases, including immune thrombocytopenic purpura, autoimmune thyroid disease, and immune he-

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\includegraphics[width=\textwidth]{fig1.jpg}
\caption{Vesicular lesions on leg.}
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\begin{figure}[h]
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\includegraphics[width=\textwidth]{fig2.jpg}
\caption{Vesicular lesions on back.}
\end{figure}
notice that the expression of pemphigus-like antibodies by tumor cells of patients with lymphoma or myeloma has been described. This could not be evaluated in this patient, but one could hypothesize that direct stimulation of B-cells by IL-2 or α-IFN could lead to overexpression of such a clone. It is also possible that the effects of IL-2 or β-IFN on the immunoregulatory functions of T-cells could lead to autoantibody expression. Further investigations will be required to establish the mechanisms involved.

REFERENCES