

out preceding bullous lesion and healed after oral corticosteroids (5, 6).

In our patient the titre of circulating anti-ICS antibodies was low, which might indicate a prolonged initial phase of PV before generalized development of bullae. The massive plasma cell infiltrate seen in the lesional upper dermis may be a factor for the localization of the lesions. Another possibility is that an unknown mechanism prevents the generalization of PV, resulting in the unique features described above. Since acanthosis was seen histologically, the diagnosis of pemphigus vegetans is also possible.

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Interferon Alpha-2a Monotherapy for Necrobiotic Xanthogranuloma

Sir,

Necrobiotic xanthogranuloma (NX) is a rare histiocytic disorder, which was first described as a distinct entity by Kossard & Winkelmann in 1980 (1). NX is characterized clinically by indurated xanthomatous or violaceous nodules and plaques that occur mostly on the trunk and the periorbital area (2). Since, in some cases, involvement of internal organs has been clearly documented (3), NX should be regarded as a systemic disease. Under light microscopy the cutaneous lesions reveal palisading granulomas in the dermis and subcutis, with numerous giant cells, of foreign body and Touton types, associated with areas of necrobiosis or hyalinized connective tissue (4). NX is commonly associated with myeloproliferative disorders, particularly multiple myeloma and lymphoma, paraproteinaemia, increased sedimentation rate and serum immunoglobulin levels, anaemia and leukopenia (5). Various therapeutic approaches, including cytotoxic agents, radiotherapy, surgical excision and plasmapheresis, have been employed in the management of NX with varying success (4).

In view of the recently reported favourable therapeutic results of the combined application of prednisone and interferon alpha in NX (6), we investigated the efficacy and safety of subcutaneous recombinant interferon α -2a monotherapy in a case of NX.

CASE REPORT

An 82-year-old Caucasian man was referred to the Department of Dermatology, University of Patras, Greece, for evaluation and treatment of cutaneous lesions that had developed over a 3-year period. On examination, multiple firm, painless, yellowish-red nodules and plaques, with an atrophic and teleangiectatic centre, were seen on his upper chest and back (Fig. 1A). There was no evidence of lymphadenopathy or hepatosplenomegaly and the remainder of the

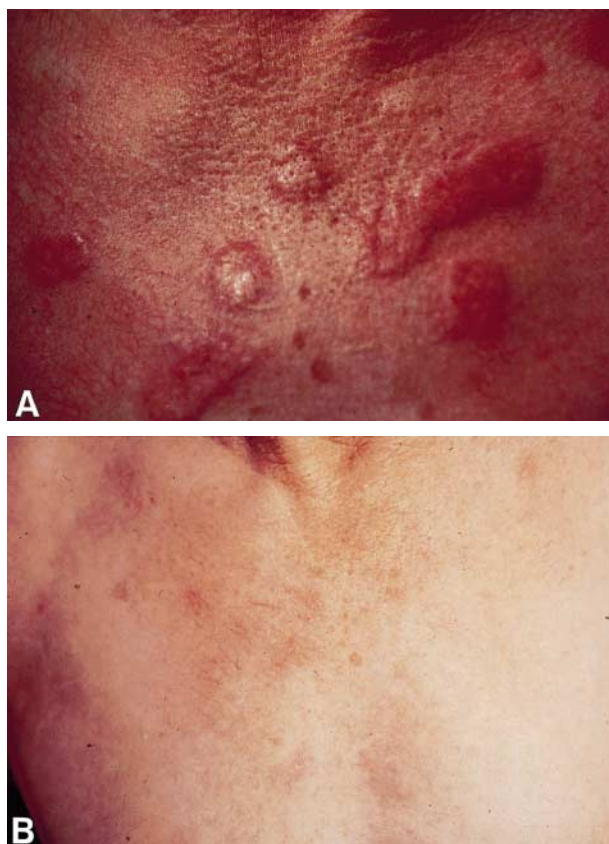


Fig. 1. Clinical presentation of yellowish-red nodules and plaques affecting the chest (A) before and (B) 4 months after start of subcutaneous recombinant interferon alpha-2a monotherapy.

physical examination was unremarkable. Neurological, ophthalmological, cardiological, computer tomography and X-ray examinations revealed no abnormal findings. The results of all routine laboratory investigations, including serum lipid and glucose levels, glucose tolerance test, serum protein electrophoresis and immunoelectrophoresis were within normal limits.

Biopsy specimens derived from the lesional skin were stained with haematoxylin-eosin, periodic acid-Schiff (PAS), alcian blue, Perls' iron, Congo red, Ziehl-Nielsen, Sudan IV and with monoclonal antibodies (CD₃, CD₄, CD₈, Mac 387 and S-100, vimentin) using the avidin-biotin immunoperoxidase method (Vectastain ABC Kit, Vector Laboratories, Burlingame, CA, USA). The histological pattern was characterized by extensive necrobiotic areas that were surrounded by granulomatous infiltration and contained several cholesterol clefts. Under polarized light microscopy, no foreign bodies could be detected within the necrobiotic areas. The granulomas comprised a mixture of epithelioid cells, foamy histiocytes, large and bizarre angulated multinucleated giant cells of both the Touton and foreign body types and lymphocytes. Sudan IV and PAS stains were positive in several giant cells and in dermal histiocytes; all other histochemical stains were negative in the cytoplasm of infiltrating cells. The latter revealed the following immunohistochemical profile: CD₃=+; CD₄=++; CD₈=+; Mac 387=+++; S-100=-; vimentin=+. Histiocytes revealed a marked positive reaction to antibody Mac 387, which was non-reactive with the epithelioid and the multinucleated giant cells. Cultures of fresh lesional skin for bacteria, acid-fast bacilli and fungi were negative.

Written consent was obtained from the patient subsequent to a thorough explanation of the possible therapeutic efficacy and toxicity of interferon alpha. He was then injected subcutaneously with 6 × 10⁶ IU/day human recombinant interferon alpha-2a (Roferon, Roche Hellas SA, Athens, Greece) three times a week over a period of 4 months. After the first 2 weeks of treatment, the lesions started flattening and within 4 months they showed complete remission in both clinical (Fig. 1B) and histological terms. Interferon administration was generally well tolerated by the patient, who experienced occasional fever, myalgia, fatigue and chills subsequent to injection of the drug. Apart from a temporary decrease in white blood cell count, to as low as 3,400/ml all laboratory variables remained unaltered during interferon administration. Twenty-two months after completion of therapy the patient remains well with no evidence of relapse.

DISCUSSION

We describe here a patient who had cutaneous NX without paraproteinaemia and who showed complete remission after a 4-month interferon alpha-2a monotherapy.

The cutaneous lesions of our patient were characteristic for NX in clinical, histological and immunohistochemical terms. Our other major clinical diagnostic considerations included necrobiosis lipoidica, the adult form of juvenile xanthogranuloma, papular xanthomas and multicentric reticulohistiocytosis. In necrobiosis lipoidica, however, both the necrobiosis and the granulomatous infiltrate are less extensive and more superficial than in NX, which additionally reveals atypical foreign body and Touton giant cells (7, 8), as demonstrated in the lesions of our patient. Juvenile xanthogranuloma, papular xanthomas and multicentric reticulohistiocytosis could be ruled out, since, apart from the differences in clinical terms, no necrobiosis occurs in these conditions.

Although paraproteinaemia is the most consistent laboratory finding in NX (1), in 20% of the cases reviewed by Mehregan & Winkelmann (4), in which protein electrophoresis was performed, no paraproteinaemia was found. In the case described here, paraproteinaemia was missing prior to

and during interferon therapy. However, since paraproteinaemia, multiple myeloma and lymphoma can develop in association with NX several years after the appearance of the cutaneous lesions of the latter (9), haematological investigations were performed during the follow-up of our patient, but did not detect any abnormality.

The specific interest in our case is based on the impressive therapeutic response of the cutaneous lesions of NX to interferon alpha-2a monotherapy, which, to the best of our knowledge, is reported for the first time. In 1995, Venencie et al. (6) reported favourable therapeutic results of combined administration of oral prednisone (30 mg/day) and subcutaneous interferon alpha-2b (3 × 10⁶ IU/day three times a week) in a patient with NX resistant to either melphalan alone or in combination with prednisone. No clear conclusions can be drawn from this study with regard to the possible therapeutic value of interferon alpha in NX.

Interferon alpha is known to exert profound modulatory effects on the proliferation, differentiation and immune potential of a variety of tissues (10, 11); however, since the pathogenesis of NX is presently unknown, the mechanisms of the therapeutic action of interferon alpha in this disorder remain to be elucidated.

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