EUROPEAN JOURNAL OF DERMATOLOGY

Cutaneous necrobiotic xanthogranuloma (NXG) - successfully treated with low dose chlorambucil

European Journal of Dermatology. Volume 11, Number 5, 458-62, September - October 2001, Cas cliniques

Résumé Summary

Author(s) : Susana MACHADO, Rosário ALVES, Margarida LIMA, Irene LEAL, António MASSA, Service of Dermatology, Hospital Geral Santo António, Rua D. Manuel II, Edifício ex: Cicap, 4099-001, Porto, Portugal..

Summary : We report a case of necrobiotic xanthogranuloma in a 51 year-old white male patient presenting with a 6-year history of multiple indurated violaceous nodules and plaques involving the eyelids, trunk and extremities. He had an associated paraproteinemia (Ig G lambda), elevated sedimentation rate, cryoglobulinemia and hypocomplementemia. No extracutaneous involvement was detected. He was successfully treated with chlorambucil (2 mg/d for 7 months), leading to disappearance of all skin lesions.

Keywords : necrobiotic xanthogranuloma, paraproteinemia

Pictures

ARTICLE

Necrobiotic xanthogranuloma (NXG) with paraproteinemia was first described as a distinct clinical entity in 1980 by Kossard and Winkelmann [1]. Before that, cases of atypical multicentric reticulohistiocytosis with paraproteinemia [2], atypical xanthoma disseminatum [3] or atypical forms of necrobiosis lipoidica diabeticorum [4], could be possible cases of NXG. Approximately 60 cases of NXG have been reported since then, most associated with Ig G monoclonal gammopathy but with an unclear causal relationship.

Cutaneous lesions are typically yellow-red to violaceous nodules and plaques, characteristically involving the periorbital area, face, trunk and extremities.

We report a case of a patient with a long standing disease without extracutaneous involvement, that responded positively to low-dose chlorambucil.

Case report

Disease presentation

A 51 year-old male white farmer had a 6-year history of multiple firm violaceous papulonodules on the

trunk and arms. The patient was otherwise asymptomatic. Dermatological examination revealed about 20 red to violaceous plaques *(Fig. 1)* in an asymmetric distribution, on the neck and trunk (the biggest one at the right supraclavicular area, 12 cm long). The smallest lesions were red-brown nodules on the limbs. Some plaques showed a central yellow-red colour, with telangiectasias and xanthomatization. A 0.8 cm diameter nodule was noted on the left inferior eyelid. Xanthelasma on the eyelids and periferical nerve enlargement were also observed. The rest of the physical examination was normal.

Cutaneous histopathological findings

Three cutaneous biopsies of different lesions were performed. A prominent feature in all biopsy specimens was the presence of a histiocytic infiltrate and aggregated epithelioid cells from the middle dermis through subcutis. There were numerous multinucleated giant cells, which were frequently of the Touton type, foam cells and atypical foreign body giant cells *(Fig. 2)*. Two specimens contained focal areas of cholesterol clefts and hyaline necrobiosis marginated from the surrounding granuloma *(Fig. 3)*.

Laboratory findings

Laboratory examination revealed elevated sedimentation rate (119 mm/hr, normal < 10 mm/hr) and B2 microglobulin (3,438 ng/ml, normal < 1,900 ng/ml); platelets and total white blood cell counts were below normal (platelets = 123 x 10^3/µl; WCC = 3.30 x 10^3/µl; differential count: 36.3% lymphocytes, 49% neutrophils); haemoglobin was normal (14.1 g/dl); protein electrophoresis showed a monoclonal gammopathy of the Ig G lambda type (Ig G = 3,160 mg/dl, normal 793-1,590 mg/dl). Bence-Jones proteins were not recovered in urine. Iliac crest bone marrow aspirate revealed a normocellular marrow with 4% plasma cells (76% of which showed an abnormal imunophenotype: $CD38^+$, $CD\ 138^+$, $CD56^+$, $CD19^-$) and bone marrow biopsy showed 5 to 10% lambda monoclonal plasma cells. Serum lipids (triglycerides = 112 mg/dl, normal 40-160 mg/dl; total cholesterol = 125 mg/dl, normal < 200 mg/dl), liver tests, creatinine and glucose tolerance test were normal. There was cryoglobulinemia (372 mcg/ml, normal < 40 mcg/ml) Ig A, Ig G and Ig M type, without monoclonality or rheumatoid factor activity. The complement profile revealed subnormal levels of C1q (1 mg/dl, normal 12.4-19 mg/dl), C4 (3 mg/dl, normal 12-42 mg/dl) and CH50 (classic pathway 8.0 U/ml, normal >19.2 U/ml; alternative pathway 1.4 U/ml, normal > 2.8 U/ml), but elevation of C3d (1.140 mg/dl, normal < 0.55 mg/dl). Levels of C3 (139 mg/dl, normal 81-167 mg/dl) and esterase inhibitor C1 (36.9 mg/dl, normal 31.9-38.5 mg/dl) were normal.

Extracutaneous disease study

Chest and skeletal x-ray films were normal; chest-abdominal-pelvic CT scan showed homogeneous splenomegaly (150 mm), without other alterations. Electrocardiogram and echocardiogram were normal. Clinical ophthalmological examination did not reveal abnormalities.

Nerve biopsy showed a demyelinating neuropathy, without acid-fast bacilli or granulomas.

Treatment

The patient was treated with low dose chlorambucil (2 mg/day) for 7 months, resulting in progressive flattening of the lesions *(Fig. 4)*, with eventual disappearance of all skin lesions. The paraprotein spike has persisted unmodified during all the treatment and follow-up of the patient. There was no complication with treatment, and no recurrence in 9 months of follow-up.

Discussion

Necrobiotic xanthogranuloma is characterized by peculiar clinical and histopathological findings *(Table I)*. It appears to have no sex predilection and the average age of appearance is 56 years (range 17 to 85 years) [5]. Skin lesions usually occur on the head (frequently the periorbital region), trunk and

extremities. Early lesions are indurated red to violaceous papules or nodules, that enlarge to plaques with a xanthomatous color. Infiltrated plaques may show telangiectasias and central clearing or atrophy, with ulceration [5]. The clinical appearance of the lesions observed in our patient was very typical, but ulceration was not observed.

Typical history consists of a granulomatous dermal and subcutaneous infiltrate with histiocytes, foam cells, Touton and foreign body giant cells; a hyaline necrobiosis and cholesterol clefts [6]. All of these findings were present in our case. In spite of typical histopathologic features of NXG, Mehregan and Winkelmann recommend three biopsy specimens from separate lesions in different locations [5].

Various reports have documented the association with extracutaneous involvement including the eye (conjunctivitis, keratitis, scleritis, episcleritis, iritis, uveitis, glaucoma, ptosis, ectropion, cataracts), upper respiratory tract (presenting hoarseness or painful nodules), granulomatous infiltration of the lung, skeletal muscle, kidney, hepatic and splenic granulomas, necrobiotic lesions of the intestine, pelvic and retroperitoneal xanthogranuloma lesions [5, 7]. Some authors have advised cardiac evaluation because of the presence of myocardial NXG lesions in autopsies [7]. There was no extracutaneous involvement in our case.

According to Mehregan and Winkelmann, 80% of patients with NXG tested with protein electrophoresis were found to have paraproteinemia [5], 10% of which had multiple myeloma [1], without an obvious correlation between the severity of the hematological disease and the skin lesions [8]. Our patient had paraproteinemia but did not have evidence of myeloma.

The demyelinating neuropathy documented by nerve biopsy was probably also related to paraproteinemia.

Other associated laboratory abnormalities *(Table I)* have included: elevated sedimentation rate, anaemia, leukopenia, abnormal glucose tolerance test, cryoglobulinemia and hypocomplementemia (reduced CH50, C1q, C2, C4 and C1 inhibitor). Lipids may be elevated, normal or reduced. Many of these laboratory abnormalities were seen in our case.

The etiopathogenesis of NXG is unknown. Lipoprotein profile described in the literature of NXG are quite distinct and their relationship to XNG aetiology is not known. Our patient is normolipemic. Circulating immunoglobulins may be complexed with lipids and deposit in the skin and produce a foreign-body granulomatous reaction [9]. Complement abnormalities may contribute to immune-complex formation [10]. More recently a new possible pathogenesis of NXG was postulated: the activation of monocytes *in vivo* may contribute to the intracellular accumulation of lipoprotein-derived lipids and marked hypocholesterolemia [11].

Although there is no definitive specific therapy for NXG, alkylating agents (such as chlorambucil or melphalan) with or without glucocorticoids have been reported to induce remission of skin lesions. Resistant patients or those with severe side effects from this treatment may be subjected to other approaches [1] like plasmapheresis [12] or recombinant interferon alfa 2 b [13] *(Table I)*. Treatment with chlorambucil in our case led to total remission of the skin lesions but his paraproteinemia remained unmodified.

Article accepted on 26/3/01

REFERENCES

1. Kossard S, Winkelmann RK. Necrobiotic Xanthogranuloma with paraproteinemia. *J Am Acad Dermatol* 1980; 3: 257-70.

2. Rendall JRS, Vanhegan RI, Robb-Smith AHT, *et al.* Atypical multicentric reticulohistiocytosis with

paraproteinemia. *Arch Dermatol* 1977; 113: 1576-82.

3. Frank SB, Weidman AI. Xanthoma disseminatum: an unusual form with extension of xanthomatous changes into muscle. *AMA Arch Dermatol Syph* 1952; 65: 88-94.

4. Muller SA, Winkelmann RK. Atypical forms of necrobiosis lipoidica diabeticorum: a report of three cases. *Arch Dermatol* 1966; 93: 272-81.

5. Mehregan D, Winkelmann RW. Necrobiotic xanthogranuloma. *Arch Dermatol* 1992; 128: 94-100.

6. Finan MC, Winkelmann RK. Histopathology of Necrobiotic xanthogranuloma with paraproteinemia. *J Cutan Pathol* 1987: 92-9.

7. Umbert I, Winkelmann RK. Necrobiotic xanthogranuloma with cardiac involvement. *Br J Dermatol* 1995; 133: 438-43.

8. Mcgregor J, Miller J, Smith N, Hay R. Necrobiotic xanthogranuloma without periorbital lesions. *J Am Acad Dermatol* 1993; 29: 466-9.

9. Bullock JD, Bartley GB, Campbell RJ, *et al.* Necrobiotic xanthogranuloma with paraproteinemia: case report and a pathogenetic theory. *Ophtalmology* 1986; 93: 1233-6.

10. Hauser C, Schifferli J, Saurat JH. Complement consumption in a patient with necrobiotic xanthogranuloma and paraproteinemia. *J Am Acad* 1991; 24: 908-11.

11. Matsuura F, Yamashita S, Hirano K, *et al.* Activation of monocytes *in vivo* causes intracellular accumulation of lipoprotein-derived lipids and marked hypocholesterolomia: a possible pathogenesis of necrobiotic xanthogranuloma. *Atherosclerosis* 1999; 142: 355-65.

12. Finelli L, Ratz J. Plasmapheresis, a treatment modality for necrobiotic xanthogranuloma. *J Am Acad Dermatol* 1987; 17: 351-4.

13. Venencie P, Le Bras P, Toan N, *et al.* Recombinant interferon alfa-2b treatment of necrobiotic xanthogranuloma with paraproteinemia. *J Am Acad Dermatol* 1995; 32: 666-7.

14. Còdere F, Duane Lee R, Anderson R. Necrobiotic xanthogranuloma of the eyelid. *Arch Ophthalmol* 1983; 101: 60-3.

15. Kocsard E. Xantogranuloma necrobiotico con paraproteinemia. *Giorn It Derm Vener* 1983; 118: 219-22.

16. Holden CA, Winkelmann RK, Wilson Jones E. Necrobiotic xanthogranuloma: a report of four cases. *Br J Dermatol* 1986; 114: 241-50.

17. Macfarlane AW, Verbov JL. Necrobiotic xanthogranuloma with paraproteinemia. *Br J Dermatol* 1985; 113: 339-43.

18. Poiares-Baptista A, Gonçalo S, Figueiredo A. Xanthogranulome nécrobiotique avec paraprotéinémie. *Ann Dermatol Venereol* 1988; 115: 1147-8.

19. Venencie PY, Doukan S, Vieillefond A, *et al.* Xanthogranulome nécrobiotique avec paraprotéinémie. *Ann Dermatol Venereol* 1992; 119: 825-7.

20. Tomasini C, Aloi S, Depaoli M, *et al.* Xantogranuloma necrobiotico. *Giorn It Derm Vener* 1993; 128: 61-5.

21. Winkelmann RK, Litzow MR, Umbert IJ, *et al.* Giant cell granulomatous pulmonary and myocardial lesions in necrobiotic xanthogranuloma with paraproteinemia. *Mayo Clin Proc* 1997; 72: 1028-33.

22. Johnston KA, Grimwood RE, Meffert JJ, *et al.* Necrobiotic xanthogranuloma with paraproteinemia: an evolving presentation. *Cutis* 1997; 59: 333-6.