Acta Derm Venereol (Stockh) 1994; 74: 221–223

Generalized Normolipemic Plane Xanthomatosis Associated with Relapsing Polychondritis

TATSUO YOSHIMURA, SETSUYA AIBA, TAKAYOSHI TADAKI and HACHIRO TAGAMI

Tohoku University School of Medicine, Department of Dermatology, Sendai, Japan

Generalized normolipemic plane xanthomatosis is a rare cutaneous disorder, frequently associated with reticuloendothelial diseases and some disorders with inflammation. Relapsing polychondritis is also a rare disease that shows an association with various immune-mediated diseases. We report a case of generalized normolipemic plane xanthomatosis associated with relapsing polychondritis in a 56-year-old Japanese man. We have already reported the clinical picture of relapsing polychondritis as well as an increase in urinary glycosaminoglycans excretion in this patient. During subsequent treatment with various immunosuppressive therapy, including prednisone, methotrexate, azathioprine, or aurothiomalate, multiple elevated yellowish erythematous plaques appeared on his neck approximately 32 months after the onset of relapsing polychondritis. Histologically, these eruptions consisted of perivascular neutrophilic infiltrate with nuclear dust and multiple foam cells among collagen bundles, compatible with those of generalized normolipemic plane xanthomatosis. This combination of two rare diseases has not been reported in the literature to our knowledge. ***Key words: immunosuppressive therapy; foam cells.***

(Accepted November 15, 1993.)

Acta Derm Venereol (Stockh) 1994; 74: 221–223.

T. Yoshimura, Department of Dermatology, Tohoku University School of Medicine, 1–1 Seiryoumachi, Aoba-ku, Sendai, 980, Japan.

Cutaneous xanthomatosis is generally accompanied by hyperlipidemia, but in a limited number of cases diffuse plane xanthomatous changes have been described in patients with normal serum lipid values and are called generalized normolipemic plane xanthomatosis (GNPX). Reticuloendothelial disorders, including multiple myeloma, chronic myeloid leukemia, eosinophilic granuloma, histiocytosis X, mycosis fungoides and Sézary's syndrome, are the conditions most frequently associated with GNPX (1–3).

Relapsing polychondritis (RP) is a rare disease of unknown etiology, manifesting itself as episodic inflammation of cartilaginous structures throughout the body. About 30% of patients with RP have evidence of an associated disease (4). Rheumatoid arthritis, Sjögren's syndrome, pregnancy, tuberculosis, myxedema, thyroiditis, ulcerative colitis, lupus erythematosus, polyarthritis nodosa, myelodysplastic syndrome, diabetes mellitus, glomerulonephritis, bronchorrhea and Reiter's syndrome are the reported concomitant conditions (5–10). We report a patient with the typical features of RP in whom GNPX subsequently developed. This association has not previously been reported.

CASE REPORT

This Japanese case of RP has already been reported by Tadaki et al. (11). Briefly, a 56-year-old man presented at our clinic with a 4-month history of recurrent edematous swelling and several subcutaneous nodules on his legs and a sudden onset of red swelling with severe tenderness in his ears. A skin biopsy specimen taken from the right auricle showed the histopathologic features of RP. No circulating antibodies against bovine type-II collagen were demonstrated. Another skin biopsy specimen taken from the subcutaneous nodule on his right arm showed a feature of vasculitis surrounded by dense dermal neutrophilic infiltrate. No deposits of immunoglobulins (IgG, IgA, IgM) or complements (C3, C1q) were detected by the direct immunofluorescence method.

Systemic prednisone 20 mg/day was effective in suppressing all the symptoms of RP, but later trials to taper the dosage always encountered the recurrence of indurated erythematous plaques. After 12 months, he developed neurosensory hearing loss, tinnitus and vertigo, non-erosive inflammatory polyarthritis, inflammation of nasal cartilage and about 32 months later, his RP became intractable. Even systemic prednisone 100 mg/day was not enough to suppress high fever as well as the advancement of the disease activity. Pulse therapy with methylprednisolone 1,000 mg could produce only a transient improvement. Methotrexate, azathioprine or sodium aurothiomalate had brought no improvement, and subsequently anemia, pneumonia, atrial fibrillation and congestive heart failure also appeared. At that time very peculiar eruptions started as multiple infiltrated yellowish erythematous plaques on his neck and upper chest. They gradually lost the yellowish tone over several days, with an increase in induration. Finally they coalesced into large elevated red plaques (Fig. 1). A histological specimen of these eruptions showed diffuse infiltration of polymorphonuclear leukocytes, mononuclear cells and plasma cells associated with abundant nuclear dust. Interestingly, in this inflammatory infiltration, there were numerous foam cells in the upper part of the dermis (Fig. 2). Factor XIIIa was positive on those cells. Thus we made a diagnosis of GNPX.

Routine laboratory data showed a decrease in red blood cells and platelet counts, elevated erythrocyte sedimentation rate, positive C-reactive protein, and increase of serum IgG (2940 mg/dl; normal 800 ~ 1800) and IgA (1062 mg/dl; normal 90 ~ 450). By immunoelectrophoresis, the patient's serum showed clearly thicker precipitation lines than normal serum against anti-IgG and anti-lambda antibody. However, the levels of serum complement were normal: CH50 (34.3 U/ml; normal 30.0 ~ 40.0), C3 (62 mg/dl; normal 53 ~ 115), C4 (26.2 mg/dl; normal 12 ~ 42). Also, the level of circulating immune complex was normal (≤ 1.5 μg/ml; normal ≤ 3). The plasma triglyceride, phos-

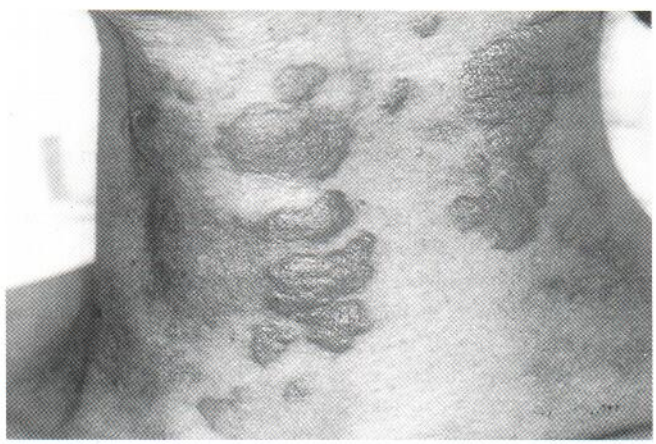

Fig. 1. Large elevated red plaques on the patient's neck.

 ISSN 0001-5555

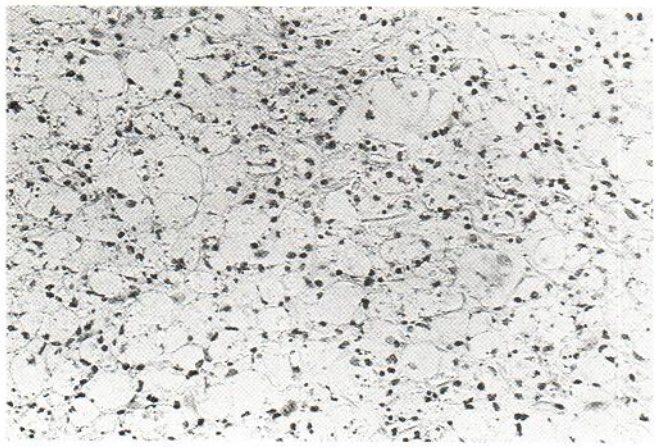

Fig. 2. Foam cells of a biopsy from the neck (hematoxylin and eosin, ×200).

pholipid and total cholesterol levels were within normal limits during the entire disease process.

Despite continuation of high dosage steroid administration (including repeated pulse therapy), the patient's condition deteriorated rapidly and he died 42 months after the onset of RP.

DISCUSSION

The clinical entity of diffuse plane normolipemic xanthomatosis was first described by Altman & Winkelmann in 1962 (12). Later, Lynch & Winkelmann categorized plane xanthomas into two groups (2). The first group, consisting of plane xanthoma together with other clinical types of xanthoma, is always associated with hyperlipemia, which is either familial or associated with liver disease, usually biliary cirrhosis. In the second group, serum lipid levels are usually normal and, if elevated, are not genetically determined or associated with liver disease. This second group can be subdivided into three groups: one group associated with reticuloendothelial diseases, another group anocited with miscellaneous coincidental diseases and a third group not associated with any systemic disorders.

The reticuloendothelial diseases which may accompany GNPX include multiple myeloma, chronic myeloid leukemia, eosinophilic granuloma, histiocytosis X, mycosis fungoides and Sézary's syndrome. Hypogonadism, rheumatoid arthritis, senile dementia, Ehlers-Danlos syndrome and previously inflamed skin such as atopic eczema, erythroderma, acrodermatitis chronica atrophicans and photosensitive eczema were reported as miscellaneous coincidental diseases (1–3, 13–21).

In our case, GNPX appeared with RP. RP is a systemic inflammatory disorder involving the cartilaginous tissues throughout the body, accompanied by occular inflammation, vestibular damage and occasional erythematous skin lesions. About 30% of the patients with RP have evidence of associated diseases (4) as reported above (5–10). However, GNPX or other types of xanthomas have never been reported in RP.

The pathogenesis of hyperlipemic and hypercholesterolemic xanthomatosis is well understood, but the pathomechanism of normolipemic xanthomatosis remains obscure. Lynch & Winkelmann (2) concluded that GNPX was a cutaneous lymphoreticular proliferation with secondary xanthomatization. Beaumont (22, 23) showed that lipoprotein-paraprotein complexes in some patients may be due to an autoantibody activity of myeloma protein against the serum lipoproteins. He postulated that the formation of an immune complex interfered with normal lipoprotein catabolism, resulting in hyperlipidemias. Two IgA and one IgG lipoprotein "complexes" were isolated from the sera of patients with myeloma. Taylor et al. (24) suggested that, having no relation to hyperlipidemias, there immune complexes may have the property of causing immunologic injury to blood vessels that follow macrophage accumulation and foam cell formation. In our case the cause of the increase in serum IgG and IgA was obscure, but by immunoelectrophoresis, the patient's serum showed clearly thicker precipitation lines than normal serum against anti-IgG and anti-lambda antibody. We think that the severe systemic inflammation caused by RP and possibly repeated usage of various immunosuppressants for its treatment might have facilitated the development of the elevation of immunoglobulin G and A levels as well as GNPX in our patient.

REFERENCES

1. Hunter RD. Normolipemic plane xanthoma and histiocytic lymphoma. Arch Dermatol 1976; 112: 1470–1471.
2. Lynch PJ, Winkelmann RK. Generalized plane xanthoma and systemic disease. Arch Dermatol 1966; 93: 639–646.
3. Altman J, Winkelmann RK. Xanthomatous cutaneous lesions of histiocytosis X. Arch Dermatol 1963; 87: 164–170.
4. Anstey A, Mayou S, Morgan K, Clague RB, Munro DD. Relapsing polychondritis: autoimmune to type 2 collagen and treatment with cyclosporin A. Br J Dermatol 1991; 125: 588–591.
5. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine Baltimore 1976; 55: 193–215.
6. Kaye RL, Sones DA. Relapsing polychondritis. Ann Int Med 1964; 55: 653–654.
7. Estes SA. Relapsing polychondritis. CUTIS 1983; 32: 471–476.
8. Silva J, Branco JC, Alves de Matos A, Canas da Silva J, Almeida O, Queiros MV. Relapsing polychondritis and Reiter's syndrome. J Rheumatol 1991; 18: 908–910.
9. Chan HS, Pang J. Relapsing polychondritis presenting with bronchorrhea. Respir Med 1990; 84: 341–343.
10. Tanaka K, Nakamura E, Naitoh K, et al. Relapsing polychondritis in a patient with myelodysplastic syndrome. Rinsho Ketsueki 1990; 31: 1851–1855.
11. Tadaki T, Aiba S, Igarashi M, Tagami H. Analysis of increased urinary acid glycosaminoglycans in a patient with relapsing polychondritis. Acta Derm Venereol (Stockh) 1987; 67: 441–445.
12. Altman J, Winkelmann RK. Diffuse normolipemic plane xanthoma. Arch Dermatol 1962; 85: 115–122.
13. Moschella SI. Xanthomatosi, associated with multiple myeloma. Arch Dermatol 1970; 102: 121–123.
14. Walker AE, Sneddon IB. Skin xanthoma following erythroderma. Br J Dermatol 1968; 80: 580–587.
15. Marks R, Wilson-Jones E. Light sensitivity and secondary plane xanthoma. Br J Dermatol 1971; 85: 297–298.
16. Feiwel M. Xanthomatosis in cryogloburinaemia and other paraproteinaemias with report of a case. Br J Dermatol 1968; 80: 719–729.
17. Lindeskog GR, Gustafson A, Enerbäck L. Serum lipoprotein deficiency in diffuse "normolipemic" plane xanthoma. Arch Dermatol 1972; 106: 529–532.
18. Schloss E, Brown J. Sézary's syndrome and generalized plane xanthoma. CMA J 1978; 118: 377–378.
19. James MP, Warin AP. Plane xanthoma developing in photosensitive eczema. A report of three cases with a discussion of a possible mechanism for lipid accumulation in plane xanthomas. Clin Exp Dermatol 1978; 3: 307–314.

20. James MP, Gold SC. Generalized plane xanthoma. Br J Dermatol 1976; 95 (Suppl 14): 50–51.
21. Thomsen RJ, Caplan RM, Bartley JA. Generalized normolipemic plane xanthoma. Arch Dermatol 1981; 117: 521–522.
22. Beaumont JL. Hyperlipidemia with circulating anti B lipoprotein auto-antibody in man: auto-immune hyperlipidemia, its possible role in atherosclerosis. Prog Biochem Pharmacol 1968; 4: 110–121.
23. Beaumont JL. Auto-immune hyperlipidemia: an atherogic metabolic disease of immune origin. Rev Eur Etud Clin Biol 1970; 15: 1037–1041.
24. Taylor JS, Lewis LA, Battle JD, et al. Plane xanthoma and multiple myeloma with lipoprotein-paraprotein complexing. Arch Dermatol 1978; 114: 425–431.