Generalized normolipemic Plane Xanthomatosis Associated with Relapsing Polychondritis

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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 aurothioglucose, multiple elevated yellowish erythematosus 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.

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Cutaneous xanthomatosis is generally accompanied by hyperlipidemia, but in a limited number of cases diffuse plane xanthomatosis 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, myeloma, thyroiditis, ulcerative colitis, lupus erythematosus, polyarthritis nodosa, myelodysplastic syndrome, diabetes mellitus, glomerulonephritis, bronchocerebral, 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 swellings 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 polyarthalgia, 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 aurothioglucose 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 histologic 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 900 ~ 1800) and IgA (1062 mg/dl; normal 90 ~ 450). By immunoelectron microscopy, 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.
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 nonmolipemic 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 lipids 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 associated with miscellaneous coincidental diseases and a third group not associated with any systemic disorders.

The reticuloendothelial diseases which may accompany GNXP 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, GNXP appeared with RP. RP is a systemic inflammatory disorder involving the cartilaginous tissues throughout the body, accompanied by ocular 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, GNXP or other types of xanthomas have never been reported in RP.

The pathogenesis of hyperlipemic and hypercholerolemic xanthomatosis is well understood, but the pathogenesis of normolipemic xanthomatosis remains obscure. Lynch & Winkelmann (2) concluded that GNXP 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, these 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 may have facilitated the development of the elevation of immunoglobulin G and A levels as well as GNPX in our patient.

REFERENCES