# Generalized Plane Xanthoma Associated with Monoclonal Gammopathy of Unknown Significance

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**Generalized plane xanthoma is less common and usually involves the eyelids, lateral side of the neck, upper trunk, and extremities. Lesions, however, may appear on any portion of the body. Cutaneous xanthomas may occur in hyperlipidemic and in normolipidemic states. Generalized normolipidemic plane xanthoma is often associated with multiple myeloma, other reticulo-endothelial malignancies and monoclonal gammopathy with unknown significance(MGUS).**

**We wish to report two cases of generalized plane xanthoma associated with IgG monoclonal gammopathy of unknown significance. (Ann Dermatol 9:(1)11~17, 1997).**

*Key Words* : Generalized plane xanthoma, Monoclonal gammopathy with unknown significance(MGUS)

The term "plane xanthoma" morphologically describes a group of xanthomatous lesions that appear as yellow to yellow-brown flat patches or slightly elevated plaques. The lesions vary greatly in size and may show sharply demarcated borders. When generalized, the disease is frequently associated with multiple myeloma or other reticulo-endothelial malignancies and monoclonal gammopathy with unknown significance. Among associated diseases, monoclonal gammopathy of unknown significance (MGUS)[1] occurs in 1 percent of the population over the age of 50 and in up to 10 percent over 75. About 11 percent of the patients with MGUS go on to develop myeloma but typically, patients with MGUS require no therapy because of the dangers of chemotherapy. The histological features of generalized plane xanthoma[2] include both xanthomatous and inflammatory elements. Accumulations of foamy macrophages infiltrate the dermis with a distinct perivascular accentuation, and are associated to a variable degree with a mixed inflammatory cell reaction. A few Touton giant cells may also be found.

The purpose of this report is to emphasize the need to study the clinical patterns, course and prognosis of generalized plane xanthoma associated with monoclonal gammopathy of unknown significance.

Received June 3, 1996.
Accepted for publication October 2, 1996.
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## REPORT OF CASES

**Case 1.**

A 53 year-old Korean woman first noticed asymptomatic yellowish patches on both eyelids ten years ago. Similar lesions appeared gradually on her face, neck, trunk and lower extremities. There was no bone pain, lymphadenopathy, or hepatosplenomegaly.

Physical examination revealed xanthelasma on both upper eyelids and diffuse plane, sheet like, noninfiltrative yellow to orange colored macules on the face, neck, trunk and lower extremities (Fig. 1). The Palm, sole and mucous membrane were spared.

Routine laboratory studies were within normal limits except for an elevated erythrocyte sedimen-

Annals of Dermatology
Vol. 9, No. 1, January 1997

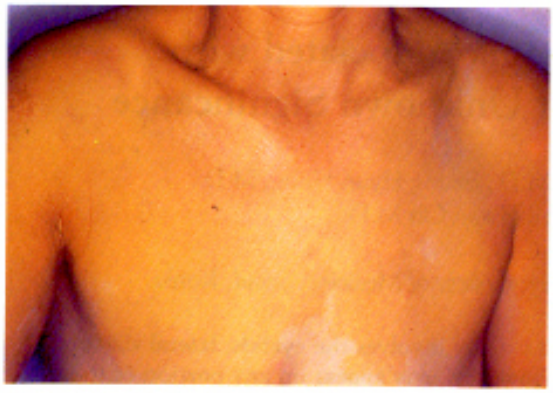


Fig. 1. diffuse plane, sheet like, noninfiltrative yellow to orange colored macules on the trunk in case 1.

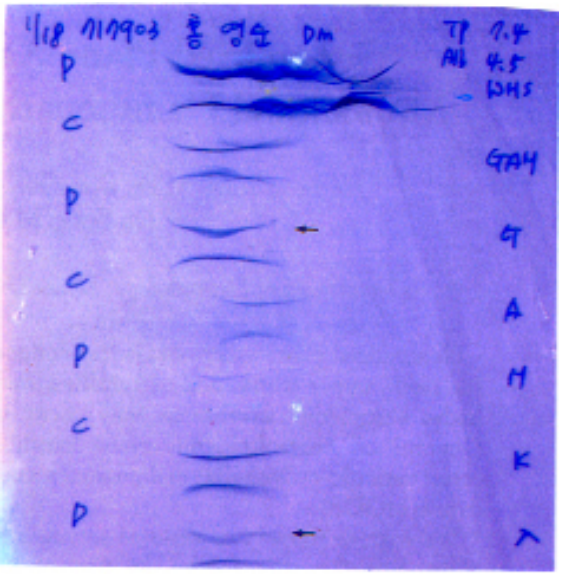
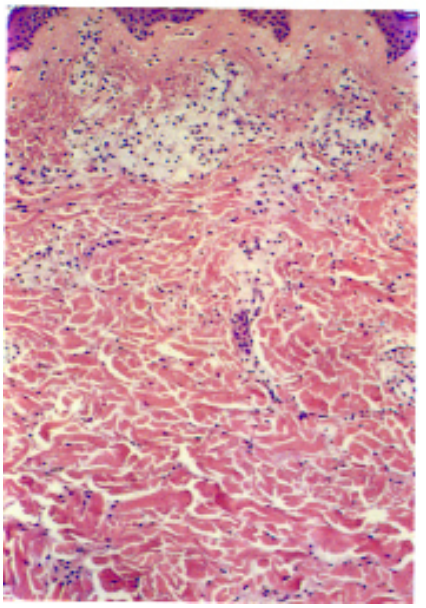


Fig. 2. serum immunoelectrophoresis showed an abnormally bowed arc on trivalent antiserum and anti-IgG and anti-lambda anti-sera. (arrows).



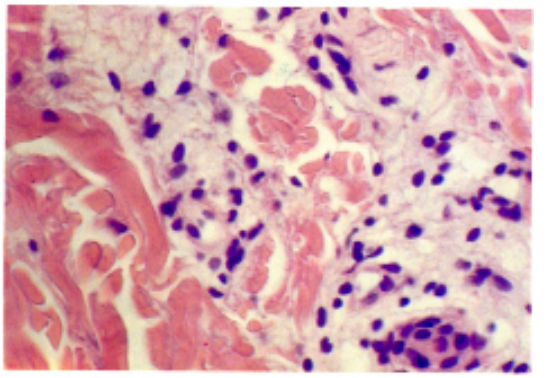


Fig. 3,4. diffuse foamy cells with single, round, centrally, placed nuclei and foamy cytoplasm in the upper dermis, especially in the perivasculat area in case 1 (H & E, ×40, ×200).

tation rate(ESR) of 56mm/h. The peripheral blood smear was normal. The total lipid concentration of fasting serum was 590mg/100ml, cholesterol 190mg%, triglyceride 86mg%, and phospholipid 218mg%. Serum lipoprotein electrophoresis show-ed normal results. The serum protein electrophoresis showed a monoclonal band on the γ-globulin region(M protein: 0.75gm/dl). The immunoelectrophoretic analysis using class- and type-specific antisera showed this paraprotein to be IgG of the lambda type(Fig. 2). The lipoprotein electrophoresis and immunoelectrophoresis findings in urine were all within normal limits.

A biopsy specimen of the skin lesion showed diffuse foamy cells with single, round, centrally placed nuclei and foamy cytoplasm in the upper dermis, especially the perivascular area(Fig. 3,4). In immunohistochemical staining for S-100, a negative finding was observed. On electron microscopic examination, the histiocytic foamy cells contained numerous lipid vacuoles and membrane limited dense bodies were seen in the cytoplasm (Fig. 5). We were not able to find the Birbeck granule. A Roentrogenogram of the skeletal series was normal. There was no family history of skin, thyroid or hematologic diseases. We reviewed several

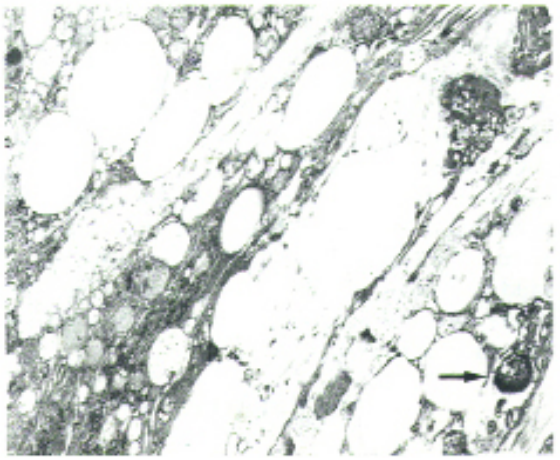


Fig. 5. On electron microscopic examination, there were numerous lipid vacuoles and membrane limited dense bodies (arrow) without Birbeck granules. ( ×8,000 ).

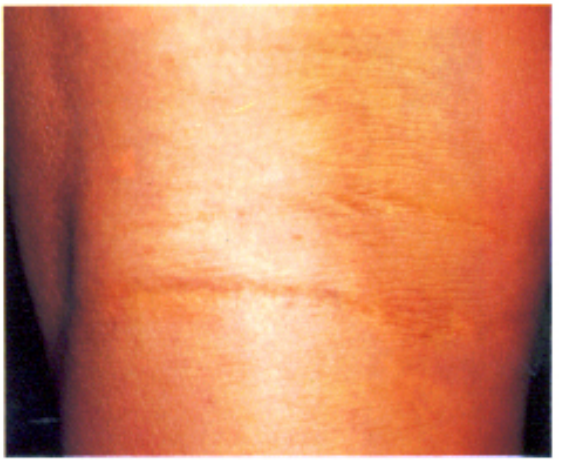


Fig. 6. diffuse patches on both popliteal areas in case 2.

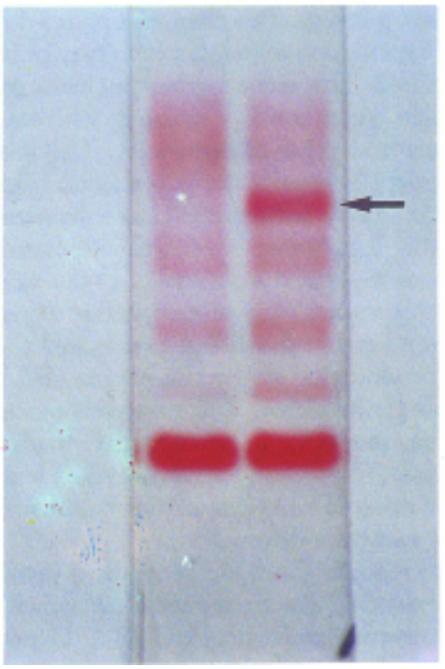


Fig. 7. serum protein electrophoresis showed monoclonal bands on the early gamma portion. (arrow) ( left ; normal control, right ; patient serum ).

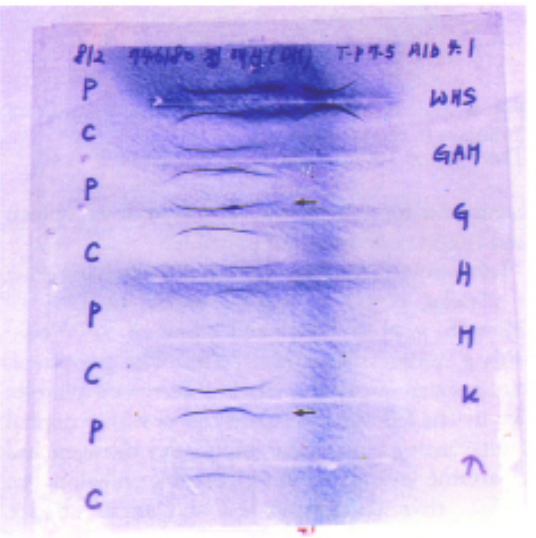



Fig. 8. In serum immunoelectrophoresis, there was an abnormally bowed arc on trivalant antiserum and anti-IgG and anti-kappa anti-serum. (arrows).

references for a correct diagnosis and method of treatment, and found that such a disease was reported as a generalized plane xanthoma without underlying abnormalities by Seo[3] in 1990. After five years, however, we confirmed by serum protein electrophoresis, immunoelectrophorisis and other laboratory tests that the patient had associated abnormalities, as well as generalized plane xanthoma.

**Case 2.**

A 61 year-old man seen at our clinic in 1995, gave a history of asymptomatic yellowish discoloration of the skin of 2 months duration.

On physical examination, several diffuse patches were seen on the right antecubital, both popliteal areas and the left thigh(Fig. 6). There were xanthe-

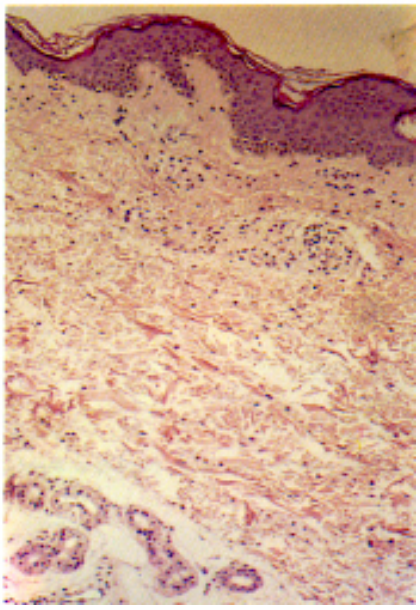


**Fig. 9.** foam cells and a mild perivascular lymphocyte infiltrates in the upper dermis.
There are no Touton-type giant cells. (H & E, ×40).

lasma and rosacea on the face. The liver, spleen and lymph node were not palpable.

Laboratory evaluation showed the following data: a platelet count of 124,000/mm$^3$, an ESR of 34mm/h, a white blood cell count of 5,800/mm$^3$ with a normal differential count. The peripheral blood smear showed a slightly decreased platelet count. The following were negative or within normal limits: fasting blood sugar, blood urea nitrogen and creatinine level, liver function tests, cryoglobulin, VDRL, thyroid function test and urinary Bence Jones protein. The total lipid concentration of fasting serum was 697mg/100ml, total cholesterol 179mg%, triglyceride 208mg%, phospholipid 193mg% and cold agglutinin titer was 1:8. The serum $\beta$2-macroglobulin level was elevated.(2.64$\mu$ g/ml) The serum lipoprotein electrophoresis pattern was within normal limits except for a triglyceride of 208mg%. The serum protein electrophoresis finding (Fig. 7) was monoclonal gammopathy on the early gamma portion.(M protein: 1.3g/dl) The urine protein electrophoresis finding also showed a monoclonal band on the early gamma portion. Serum electrophoresis for immunoglobulin showed an abnormally bowed arc on trivalent antiserum and anti-IgG and anti-kappa anti-sera (Fig. 8). Typing of the $\gamma$-globulin proved it to be an IgG type kappa light chain. A bone marrow examination showed slightly hypercellular marrow with erythroid hyperplasia and plasmacytosis(8%). The chest, skull and lumbosacral films and abdominal sonogram were normal.

A skin biopsy specimen of the lesion showed the epidermis to be normal. The dermis showed a scattered collection of lipid-laden foam cells and a mild perivascular lymphocyte infiltration(Fig. 9). There were no Touton-type giant cells. There was no immunoreaction for S-100.

## DISCUSSION

Generalized plane xanthoma can be categorized into two large groups. The first group consists of generalized plane xanthoma occurring with other xanthomatous processes such as plane, papular, and nodular lesions. This phenomenon is a direct result of hyperlipoproteinemia which may be familial or acquired. The second group includes generalized plane xanthoma associated with multiple myeloma and other malignancies. The serum in later groups is usually normolipidemic. This second group can be further subdivided into essential or idiopathic xanthoma, xanthoma associated with disease of the reticuloendothelial system and xanthoma associated with miscellaneous disease. Of the second group, the diseases associated with the reticuloendothelial system are plasma cell dyscrasia(multiple myeloma, Waldenstrom's macroglobulinemia, monoclonal gammopathy of unknown significance), chronic granulocytic leukemia, chronic myeloid leukemia, cryoglobulinemia, lymphoma, and histiocytosis X.

These reported cases are generalized plane xanthoma associated with monoclonal gammopathy of unknown significance(MGUS)[1]. Generalized plane xanthoma was first reported in Korea by Lee[2] in 1984. After that, in 1990, Seo[3] reported it as generalized plane xanthoma without underlying abnormalities. No cases of generalized plane xanthoma associated with MGUS, which we reported, can be found in domestic publications. MGUS is diagnosed according to the Durie-Salmon classification: monoclonal gammopathy, M-component level(Ig G<3.5g/dL), no bone lesions, less than 10 percent marrow plamacytosis and no symptoms. Generalized plane xanthoma associated with paraproteinemia[4,5] is a well-documented clinical abnor-

mality. In paraproteinemia, MGUS increases in frequency over the age of 60. Approximately 10 percent of these patients later develop a true immunoproliferative disorder[6]. The dermatologic disorders associated with MGUS are generalized plane xanthomatosis, discoid lupus, lichen myxedematosus, pyoderma gangrenosum and scleredema.

On histological examination, both cases showed perivascular lymphohistiocytic infiltration and foamy cells in the upper dermis. On electron microscopic examination of case 1, there were numerous lipid vacuoles and membrane limited dense bodies in the foamy histiocyte.

However, we could not find the Birbeck granule which had been described in the case reports of normolipemic papular xanthoma by Winkelmann[7]. Immunohistochemical staining for S-100 were negative.

The pathogenesis of normolipidemic or hyperlipidemic plane xanthoma associated with paraproteinemia[8,9] is unknown. Some authors[9,10] postulated that some cases of normolipidemic xanthomatosis represented reactive hyperplasias of the reticuloendothelial system of the skin, accompanied by secondary xanthomatization. This process may be elicited by a variety of factors, among which infections and trauma may play important roles. Feingold[11] hypothesized that monoclonal IgG-LDL complexes interacted with macrophage scavenger receptors, thereby resulting in the occurrence of xanthoma in the absence of hyperlipidemia. It is not clear how the immunological role of the paraprotein[12] functions in xanthoma formation. In these cases continued clinical and laboratory follow-up will be necessary to ascertain whether these disorders are limited to the skin. Beaumont[13] showed that lipoprotein-paraprotein complexing in some patients might be due to an autoantibody activity of the myeloma protein against the serum lipoproteins. He postulated that formation of immune complexes interfered with normal lipoprotein catabolism, thereby resulting in hyperlipidemia. Using 2-14C acetate, Hu and Winkelmann7 demonstrated in vitro that in plane xanthoma lipids could be synthesized in situ. It is believed that the lipid probably permeates the vessel wall and is subsequently phagocytosized by macrophages.

It is not necessary to treat MGUS so as to prevent malignant transformation because of the serious side effects of chemotherapy. Most reported cases of generalized plane xanthomatosis have progressed or remained stable, rather than tending toward spontaneous resolution.

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