

UNUSUAL NORMOLIPIDEMIC CUTANEOUS XANTHOMATOSIS: A COMPARISON OF TWO CASES ILLUSTRATING THE DIFFERENTIAL DIAGNOSIS

Chung-Hong Hu and R. K. Winkelmann

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

Abstract. A patient who developed diffuse normolipidemic plane xanthomas also presented with IgG lambda monoclonal gammopathy, hypernephroma, an unusual family cluster of leukemia (with two family members in two generations), and a unique, acquired C1-esterase inhibitor deficiency. A second patient presented with widespread normolipidemic papular xanthomas in which histiocytes containing Langerhans' granules were found. The lipid composition of the lesions of these two patients showed striking differences. Excesses of triglycerides and cholesterol ester were demonstrated in plane xanthoma, whereas phospholipids were prominent in the papular xanthoma of histiocytosis X. We present and classify these two cases to emphasize the diagnostic value of chemical and ultrastructural studies of normolipidemic cutaneous xanthomatosis.

Key words: Monoclonal gammopathy; Hypernephroma; Cholesterol esters; Phospholipids; Cutaneous xanthoma; Normolipidemia

Cutaneous xanthomas may occur in hyperlipidemic and in normolipidemic states. The hyperlipidemic state has received much attention because it is a cutaneous marker of cardiovascular and metabolic diseases. Normolipidemic cutaneous xanthomatosis consists of various clinical dermatologic entities and frequently reflects systemic disease. Diffuse normolipidemic plane xanthoma is often associated with multiple myeloma and other lymphoproliferative diseases. Xanthelasma and papular xanthomas may be the presenting sign of such systemic histiocytic diseases as xanthogranuloma, reticulohistiocytoma, and histiocytosis X. Atypical forms of xanthomatous lesions, clinical or histologic or both, are occasionally encountered. During recent years, the discovery of histiocytes containing Langerhans' granules offered a new opportunity for understanding histiocytic xanthomatous disorders on an ultrastructural level. We

wish to describe two cases of unusual normolipidemic xanthomatosis in order to emphasize the diagnostic value of chemical and ultrastructural studies of cutaneous xanthomatosis.

REPORT OF CASES

Case 1

A 68-year-old retired farmer had been in good health until 1965, when he experienced a febrile episode with non-descriptive abdominal distress and right inguinal adenopathy. Biopsy specimen of a right inguinal node was interpreted as showing reaction with bland fat necrosis, and a specimen of the liver showed hyperplasia of Kupffer cells and an increased number of mitotic figures, indicative of some regenerative activity. The true nature of the illness remained undiagnosed, and the symptoms resolved themselves without specific therapy. In April 1968, the patient underwent transurethral resection for benign prostate hypertrophy. In June 1968, he was seen for the first time at our clinic because of intermittent upper abdominal distress.

Physical examination revealed xanthelasma about the eyelids, bilaterally. Also noted were diffuse plane, sheet-like, non-infiltrative xanthomatous plaques involving large areas of the axillae, upper arms, antecubital fossae (Fig. 1), inguinal regions, and the right lower quadrant of the abdomen. The time of onset of these lesions was unknown, and there were no similar skin lesions among his family. The liver, spleen, and lymph node were not palpable. Significant physical findings included a systolic click at the apex of the heart; a cholesterol plaque in the left retina, but no other retinopathy; and bilateral otosclerosis, with moderate loss of hearing.

The nephrotomogram demonstrated a small, expanding lesion of the left kidney. A well-encapsulated tumor, found on left nephrectomy, was histologically a grade I adenocarcinoma of the hypernephroma type. After the operation, fragments of a left ureteral stone were recovered; analysis revealed that the fragments consisted of calcium carbonate and calcium phosphate.

Other abnormal findings were grade I proteinuria, grade I microhematuria, grade I pyuria, a hemoglobin level of 11.6 g/dl, an erythrocyte count of 4 380 000/mm³, an eryth-

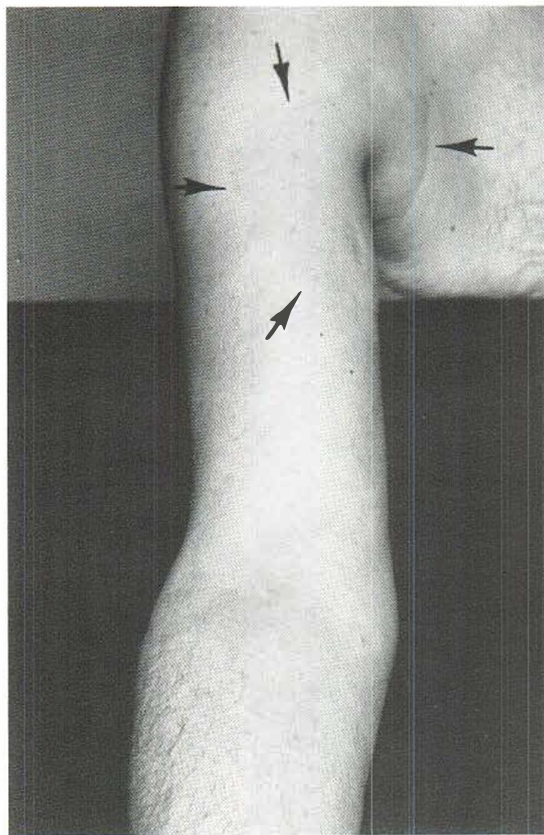


Fig. 1 (case 1). Irregular bordered plane, sheet-like xanthomatous plaques involving both sides of axillary areas. Less noticeable on antecubital fossa.

rocyte sedimentation rate of 70 mm in 1 hour, a prothrombin time of 23–26 seconds, and hypoalbuminemia with 2.58 g albumin/dl. Moderate rouleau and anisocytosis were seen on peripheral blood smear. The bone marrow aspiration revealed a non-diagnostic picture, with slightly increased mature plasma cells.

The following were negative or within normal limits: leukocyte and differential counts, serum lipids, including cholesterol (191 mg/dl), triglycerides (66 mg/dl), and phospholipids (224 mg/dl), serum lipoprotein profile, fasting blood sugar, sulfobromophthalein retention, serum creatinine, alkaline phosphatase, transaminase, amylase and lipase, Venereal Disease Research Laboratories test (VDRL), urinary Bence Jones protein, serum bilirubin, electrocardiogram, chest roentgenogram, and cholestogram.

A survey of the patient's family history revealed that one of the patient's sisters and one of his brothers had chronic lymphocytic leukemia and the patient's father had died of gastrointestinal cancer.

Since dismissal from this clinic in 1968, the patient has returned annually for a check-up. He has remained in good health except for recurrence of lower abdominal discomfort associated with moderate dysuria. In 1970, a

2.5×12 cm calculus of the urinary bladder was removed by litholapaxy.

A unique complement profile was noted when the patient was again seen in May 1972, and the size of the plane xanthomatous lesions was slightly increased. An IgG lambda-type, monoclonal gammopathy was found on serum immunoelectrophoresis. Sulfobromophthalein retention was 8% at 1 hour. The erythrocyte sedimentation rate was 58 mm in 1 hour. Bone marrow study disclosed 10% nucleated cells and many immature plasma cells. The bone survey showed degenerative arthritis of the left hip, with no lytic changes. The following were normal or negative: serum cryoglobulin, serum immunoglobulin, hemoglobin, and leukocyte and differential counts.

Total complement and complement component assays showed a low level of total complement (<5 CH₅₀), extremely low C1 (5 600 CH₅₀), C4 (<1 000 CH₅₀), and C2 (112 CH₅₀) and markedly elevated C8 (160 000 CH₅₀) and C9 (66 500 CH₅₀). The amount of C1-esterase inhibitor detected by radial immunodiffusion was low (2.56 mg/dl, normal 8 to 30 mg/dl). Levels of C3, C5, C6, and C7 were normal.

Case 2

A 25-year-old Canadian art student was first seen at our clinic in 1968. He had a 1-year history of generalized skin lesions. The lesions were elevated, firm, yellow-brown papulonodules of 3 mm to 1 cm in diameter. Their appearance was slow but progressive.

Examination revealed numerous widespread, discrete papulonodules involving the face (Fig. 2a) and more extensive on the buttocks and upper and lower extremities (Fig. 2b and c). The trunk and axillae were not involved. Although the lesions were seen over the flexural aspects of the limbs, there was no accentuation on the antecubital and popliteal regions. The lesions were discrete and showed no tendency to confluence or formation of verrucose plaques. The mucous membrane was not involved. The patient gave no history of respiratory distress or abnormal water intake or output.

The following were normal or negative: roentgenograms of the skull and chest, hemoglobin level, leukocyte and differential counts, erythrocyte sedimentation rate, VDRL, prothrombin time, serum protein electrophoresis, sulfobromophthalein retention, and urinary 17-ketosteroids. The serum lipid level was normal, the cholesterol level was 156 mg/dl; triglycerides 40 mg/dl; and phospholipids 160 mg/dl.

A therapeutic trial with nicotinic acid and clofibrate for 6 months by the patient's family physician was not effective, although local excision of some of the lesions was successful.

Study of Xanthoma Lipids Composition

Methods

After an overnight fast, specimens of xanthoma tissue were obtained, with the patient under local anesthesia (lidocaine), by use of a 6-mm punch biopsy. The subcutaneous fat was trimmed, and the tissue was homogenized. The lipids were then ex-

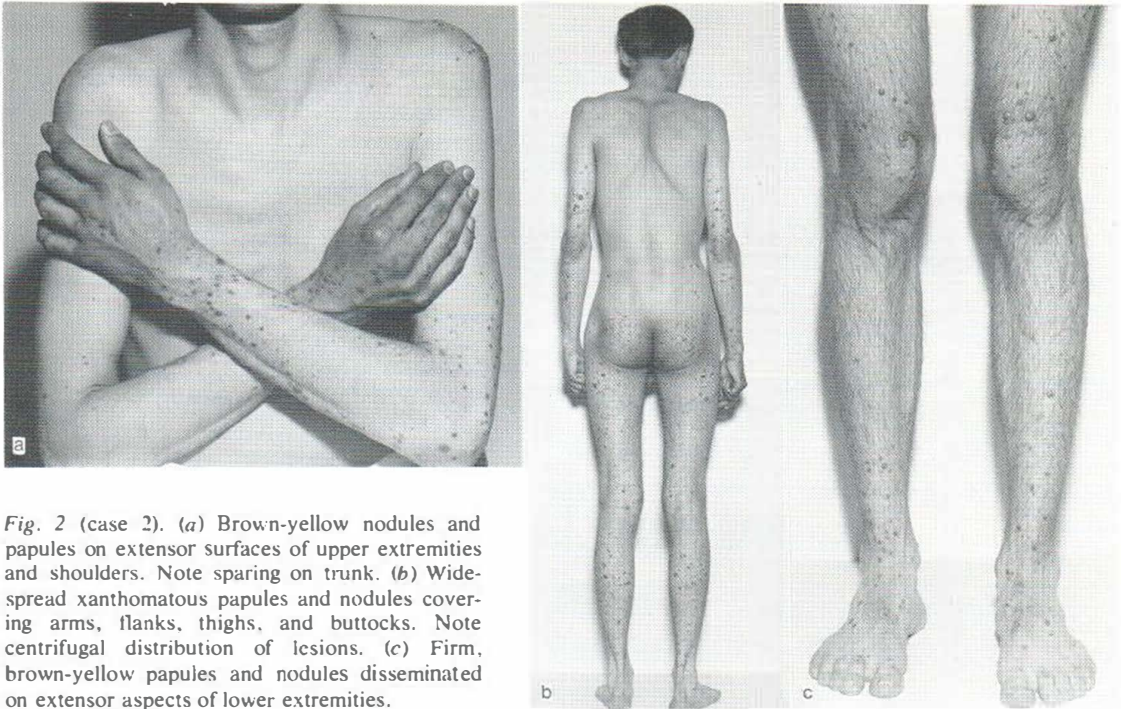


Fig. 2 (case 2). (a) Brown-yellow nodules and papules on extensor surfaces of upper extremities and shoulders. Note sparing on trunk. (b) Wide-spread xanthomatous papules and nodules covering arms, flanks, thighs, and buttocks. Note centrifugal distribution of lesions. (c) Firm, brown-yellow papules and nodules disseminated on extensor aspects of lower extremities.

tracted by means of 3 ml of chloroform methanol (2:1 by volume) three times and were fractionated by thin-layer chromatography (TLC) in Silica Gel H. Chromatograms were developed by TLC-1 (hexane/ether/acetic acid; 90:12:1) and TLC-2 (chloroform/methanol/water; 14:6:1). The lipid bands were located by exposure of the chromatograms to iodine vapor. Identification of the lipid bands was based on chromatographic mobilities (R_F).

Findings

There appeared to be an excess of triglycerides and cholesterol ester (bands 4 and 5 in Fig. 3 [Z] of left panel) in plane xanthoma of case 1. By contrast, prominence of free fatty acids (band 3 in Fig. 3 [G] of top panel) and many lipids of the phospholipid group (bands 2, 3, 4, and 5 in Fig. 3 [G] of right panel) are demonstrated in case 2.

Electron Microscopic Study

Methods

Specimens for electron microscopy were immediately trimmed into approximately 1 mm³ cubes and were fixed in 4% glutaraldehyde buffered with 4.5% sodium dimethylarsenate at pH 7.4 for 3

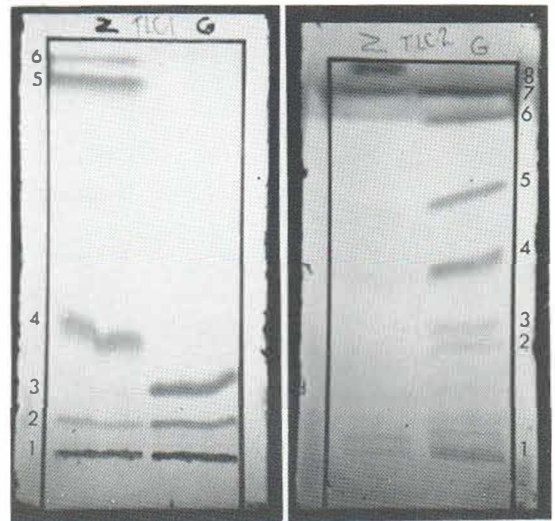


Fig. 3. Iodine-vapor-stained chromatograms of xanthoma lipids. Left panel. Developed by hexane/ether/acetic acid, 30:12:1. Left (Z) is from case 1 and right (G) from case 2. Code: 1, origin; 2, cholesterol; 3, free fatty acids; 4, triglycerides; 5, cholesterol ester; and 6, terpenoid hydrocarbons including carotenoids. Right panel. Developed by chloroform/methanol/water, 14:6:1. Left (Z) is from case 1 and right (G) from case 2. Code: 1, origin; 2, lysophosphatidyl choline; 3, sphingomyelin; 4, phosphatidyl choline; 5, phosphatidyl ethanolamine; 6, free fatty acids; 7, cholesterol; and 8, terpenes, triglycerides, and cholesterol esters.

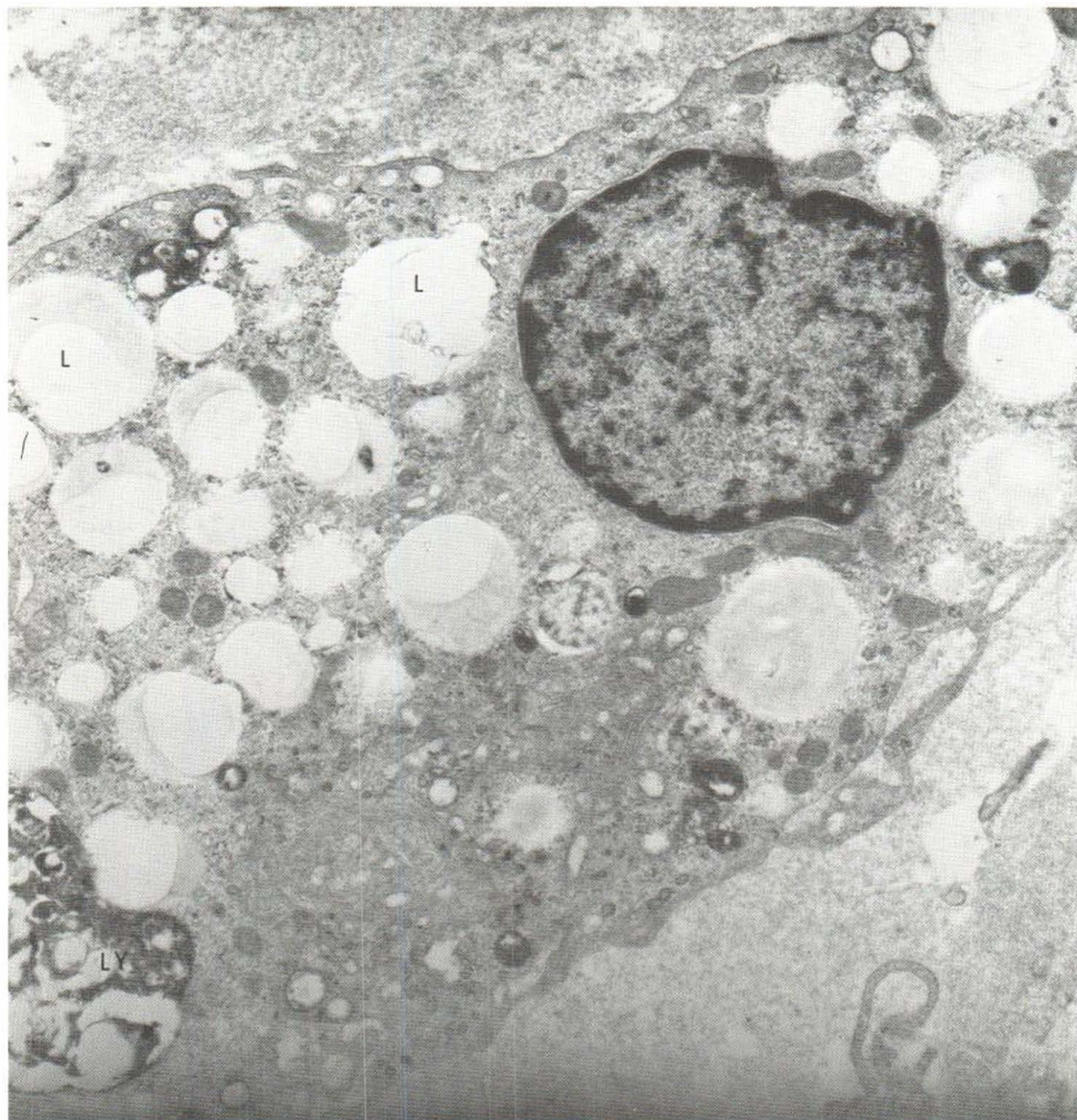


Fig. 4 (case 1). Foamy cell contains lipid vacuoles (L), lysosome structures (LY) ($\times 25\ 110$).

hours. After fixation, the blocks were dehydrated in ethanol and embedded in epoxy resin. Ultrathin sections were cut on a microtome and stained with uranyl acetate for 30 min and with lead citrate for 1½ min. All tissue specimens were examined in an electron microscope (RCA EMU 3) at 50 kV.

Findings

In both the plane xanthoma of case 1 and the papular xanthoma of case 2, foamy cells were the major

cell type of the lesions. Histiocytoid foamy cells (Fig. 4) contained numerous lipid vacuoles of varying size, dense bodies, and lysosome structures in the cytoplasm. Membrane-limited dense bodies with onion-type lamination were also seen in the cytoplasm of some foamy cells (Fig. 5). In addition to foamy cells, two significant cell types were found in papular xanthoma lesions of case 2. Typical tennis-racket-type Langerhans' granules were present in some histiocytes (Fig. 6) that had no lipid

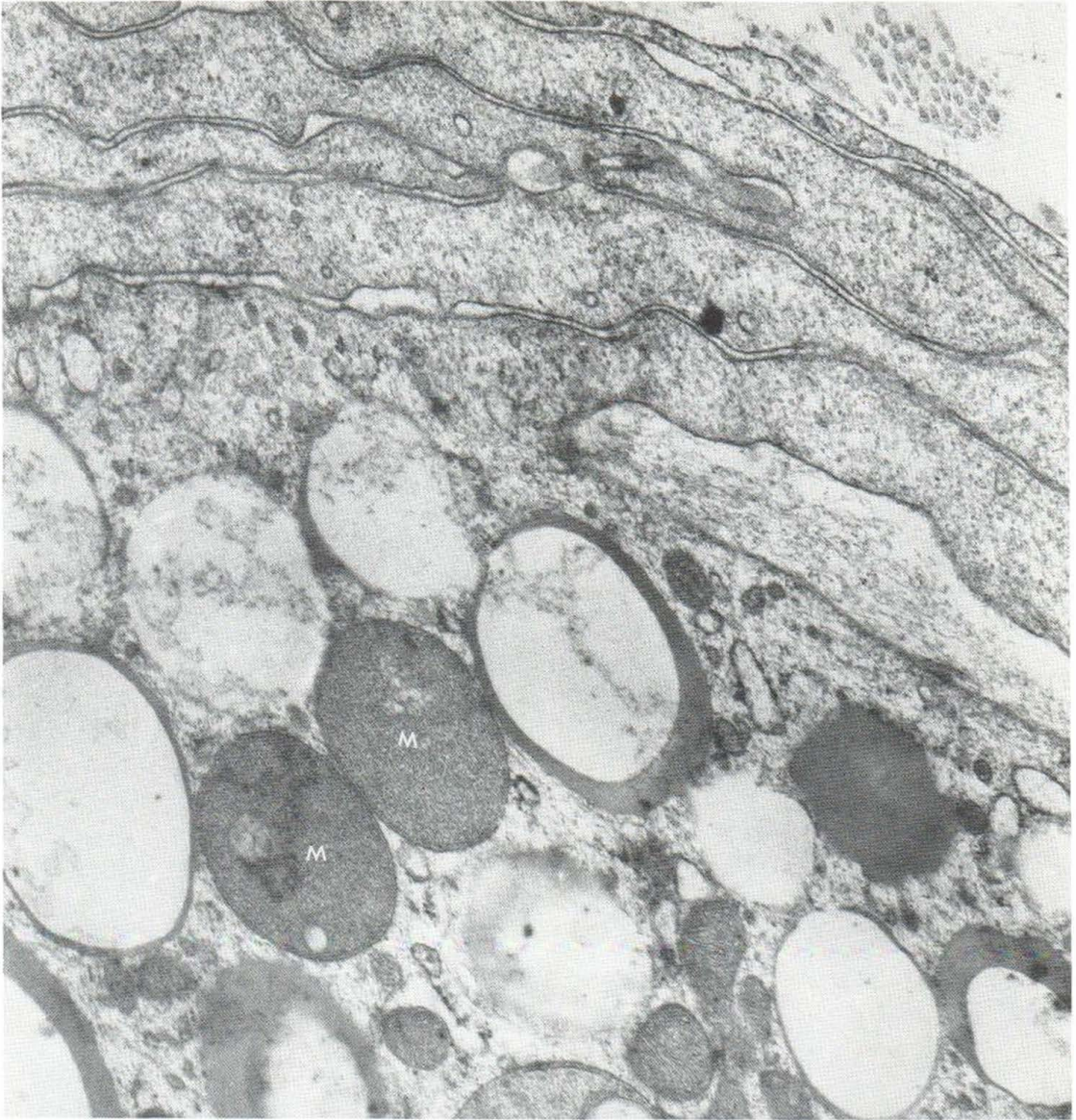


Fig. 5 (case 1). Membrane-limited dense bodies with onion lamination (M) in cytoplasm of foamy cells ($\times 56\,455$).

vacuoles in the cytoplasm. Schwann cells showed numerous lipid vacuoles and giant bodies with lipid granules (Fig. 7).

COMMENT

In case 1, the family cluster of malignant disease over three generations is striking. It consists of two cases of leukemia, one case of gastrointestinal tract cancer, and one case of triple disease (hypernephroma, benign monoclonal gammopathy,

and diffuse normolipidemic plane xanthoma). Together with the unique complement profile evidenced by C1-esterase inhibitor deficiency, this patient presents a most interesting syndrome.

The association of normolipidemic cutaneous plane xanthoma with paraproteinemia (3, 13, 24, 31) and multiple myeloma (27, 30) has become well known and was evident by the evolution of the clinical course in our case 1. Cases of normolipidemic plane xanthoma occurring con-



Fig. 6 (case 2). Histiocytes in papular xanthoma lesion show typical Langerhans' granules (arrows) ($\times 27\,920$).

comitantly with mycosis fungoides, lymphocytoma (41), and light sensitivity with xanthomatous lesions confined to the face (28) have been reported. Lymphedema (6, 42), erythroderma (40), hypogonadism, myasthenia (38), anetoderma (15), and Ehlers-Danlos syndrome (7) also have been noted in patients with normolipidemic plane xanthoma. Multiple myeloma also may occur in patients who are hyperlipidemic (5, 12, 16, 24, 26, 29, 32). To the

best of our knowledge, the occurrence of carcinoma in plane xanthoma has not been reported hitherto. To what extent hypernephroma was related to normolipidemic plane xanthoma in our case 1 is not known.

The presence of an unusual complement profile consisting of C1-esterase inhibitor deficiency, decreased concentrations of C1, C4, and C2, normal C3, and increased C8 and C9 is another interesting

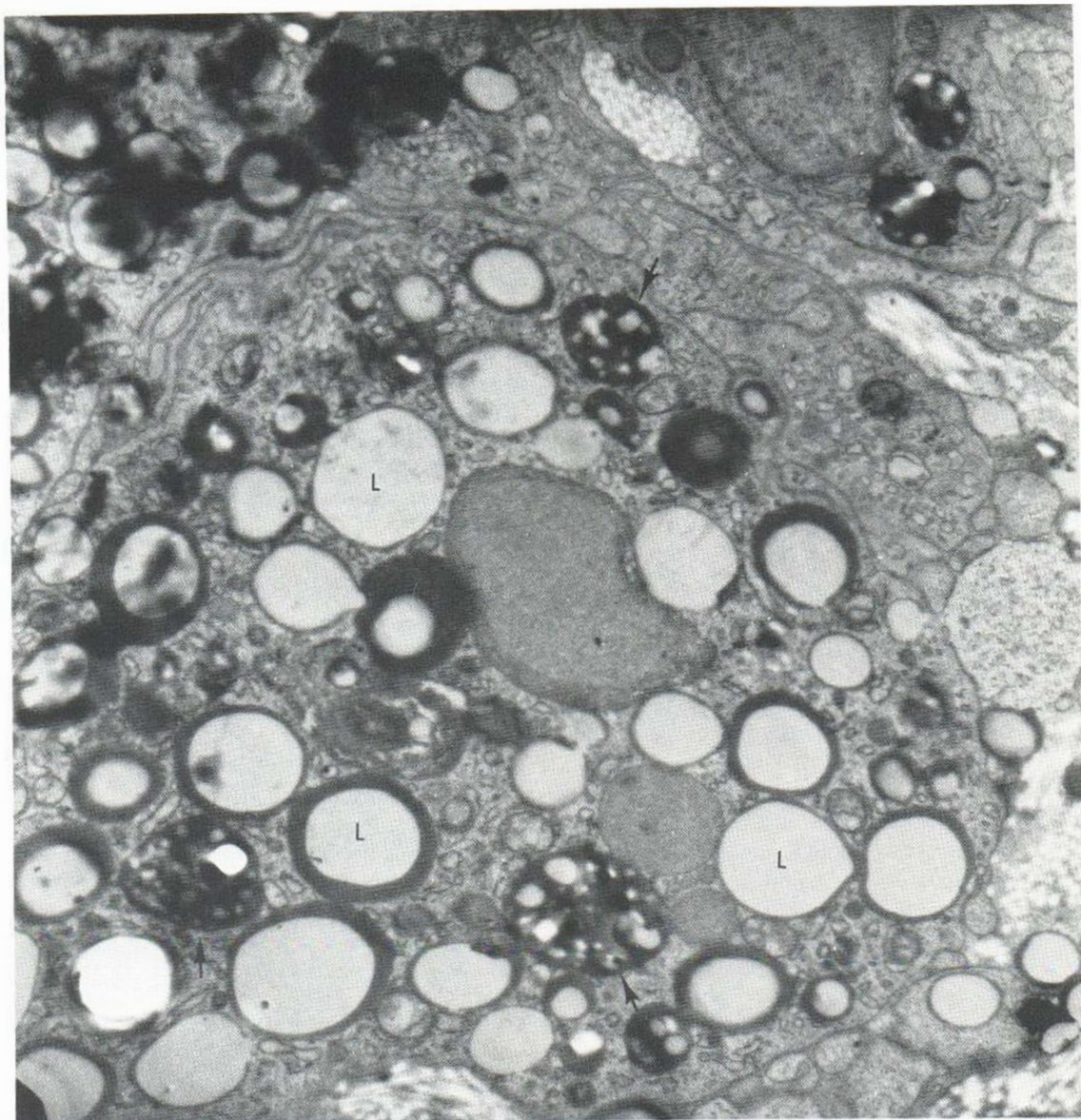


Fig. 7 (case 2). In cytoplasm of Schwann cell of papular xanthoma lesions, lipid vacuoles (L), giant bodies with lipid granules (arrows) ($\times 26\,050$).

feature in our case 1. Neither the patient nor members of his family had a history of angioedema-like symptoms. This complement profile is similar to that seen in patients with hereditary angioneurotic edema, except that, in the latter, C1 and C9 are normal. Such acquired C1-esterase inhibitor deficiency has recently been described in two patients with lymphosarcoma (8), and we believe that our case 1 represents another such relationship. We

have also observed this C1-esterase inhibitor deficiency syndrome with angioedema in an adult who developed lymphosarcoma.

Considering the clinical, genetic, and immunologic findings, we believe that our patient in case 1 has a strong potential for developing another malignant disease. We have observed him closely for 5 years, and the eventual outcome of this case will add more significant information. Progressive plas-

macytosis may indicate the direction of this disease.

The second patient illustrates the difficulty frequently encountered in diagnosing histiocytic xanthomatosis lesions. The discrete small lesions without evidence of confluence, the lack of flexural accentuation, and the absence of mucous membrane involvement—all constitute evidence against the diagnosis of xanthoma disseminatum. The patient did not develop diabetes insipidus, which may be seen in xanthoma disseminatum. The demonstration of histiocytes containing Langerhans' granules in the xanthoma papules of this patient provides additional evidence to support the concept of a broad range of histiocytosis X disorders.

Some authors considered xanthoma disseminatum and juvenile xanthogranuloma as formers frustes of histiocytosis X, whereas others consider them separate entities (14, 34, 39). Rarely, cases of histiocytosis X with cutaneous lesions show characteristics (clinical or histologic, or both) of xanthomatous histiocytic proliferations such as xanthoma disseminatum, juvenile xanthogranuloma (1), and reticulohistiocytoma (unpublished data). Recently, Hashimoto & Pritzker (19) described an infant who had Langerhans' granules in the lesions as having reticulohistiocytoma cutis; we would classify their case as one of histiocytosis X.

Since Basset et al. (2) first found histiocytes containing Langerhans' granules in osseous and pulmonary lesions of histiocytosis X in 1966, the list of disease entities with Langerhans' granule-containing cells has expanded. Thus far, Langerhans' granule-containing cells have been found in cutaneous (10, 17, 18, 25), pulmonary, osseous lesions (2), and lymph nodes (18, 21) of histiocytosis X; circulating cells of monocytic leukemia (36) and leukemic reticuloendotheliosis (4, 33); cutaneous lesions of reticulum cell sarcoma (20) and lymphomatoid papulosis (35); cutaneous lesions of malignant histiocytosis of Rappaport (22); and familial lipochrome histiocytosis (11). More recently, Langerhans' granule-containing cells in histiocytic medullary reticulosis were reported (9).

A decade ago, one of us (R. K. W.) proposed the concept of a broad spectrum of histiocytic proliferative disorders. The demonstration of Langerhans' granule-containing cells by Basset et al. (2) and many others supports this concept. We believe our case of atypical generalized papular xanthomas

with Langerhans' granule-containing cells is an additional example.

The qualitative study on xanthoma lipids of our two patients is in agreement with those by others in that the major lipid is a cholesterol ester. However, triglycerides were prominent in our first patient, who had plane xanthoma, and phospholipids were prominent in the second patient, who had generalized papular xanthoma. Studies done by others on xanthelasma palpebrarum (23) and hyperlipidemic plane xanthoma (24) did not demonstrate prominence of triglycerides in such lesions. Increased amounts of phospholipids and glycosphingolipids have been found in hepatic tissue loading with sea-blue histiocytes (37). Additional study of the histiocytic lesions as in histiocytosis X, which become xanthomatous, may indicate that phospholipids are important in this type of disease.

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Chung-Hong Hu, M.D.
Mayo Clinic
200 First Street SW
Rochester, Minnesota 55901
USA