Case Report

Adult Xanthogranulomatous Intracranial Lesion Involving Familial Hypercholesterolemia

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A 35-year-old man was admitted because of loss of hearing in the left ear. The patient had been known to have familial hypercholesterolemia for at least 12 years. Computerized axial tomography of the brain showed a large tumor occupying in the left mastoid region. Surgical intervention revealed xanthogranuloma, histologically. Xanthogranuloma is classified as a kind of normocholesterolemic xanthomatoses. Hypercholesterolemia with adult xanthogranuloma (AXG) is extremely rare. Moreover intracranial involvement with AXG has been reported in only one previous case. We wish to report on the possibility of a new syndrome that has characteristics common to primary xanthomatoses, entities which have heretofore been considered etiologically distinct.

Key words: Adult xanthogranuloma (AXG), Familial hypercholesterolemia, Intracranial lesion, Juvenile xanthogranuloma (JXG), Xanthomatosis, Xanthoma

The first case of adult xanthogranuloma (AXG) was reported by Gartmann in 1963 (1). Xanthogranuloma is a disease characterized by benign xanthoma-like skin lesions and classifies as a kind of primary normocholesterolemic xanthomatoses. Intracranial lesion is extremely rare and we were able to find only one prior report of a patient with this kind of involvement (2). We now wish to report a case of AXG that involved intracranial lesion, and that moreover was accompanied with familial hypercholesterolemia.

The purpose of this report is A) to present the history of our rare case, B) to review the other reported case intracranial involvement associated with hypercholesterolemia, C) to emphasize the emergence of a new syndrome which is not consistent with previously classified forms of xanthomatoses and D) to suggest the etiology of hypercholesterolemic AXG involving intracranial lesion.

CASE REPORT

A 35-year-old man was admitted to Jikel Hospital for investigation of hyperlipemia. From the age of nine years old, he had noted the development of yellow-orange lumps over the knees. Three years after this initial discovery, later, he noted additional lumps over the elbows, and small nodules forming on the extensor tendons of both hands and feet. About 12 years ago hyperlipidemia was pointed out and diagnosis of familial hypercholesterolemia was made. At that time treatment was not undertaken. About one year ago, loss of hearing in the left ear appeared. Computed axial tomography of the brain revealed a large area of destruction in the left mastoid region. A presumptive diagnosis of carcinoma of the left mastoid process involving extensive invasion of surrounding bones was made. Two months prior to the patients admission for investigation to exercise the affected area was undertaken and a diagnosis of xanthogranuloma was made.

Past history is unremarkable except for inguinal herniation at age nine and diagnosis of sponge kidney at age 26.

The patient’s father had hypercholesterolemia from The Third Department of Internal Medicine, The Jikei University, School of Medicine, Tokyo

Received for publication May 2, 1989.
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Yamada et al. and palpebral xanthoma. The patient's mother and her siblings had hypercholesterolemia (type IIa), diabetes, palpebral xanthoma and heart disease. The patient's brother and sister also have hypercholesterolemia (type IIb) (Table).

Physical examination showed a man of average physique whose complaints were those of impaired hearing and angina. Examination of the head revealed the elevation of the occipital bones (Fig. 1). The eyes, the ears, the nose and mouth were not remarkable. Examination of the neck was within normal limits. The chest was clear to percussion and auscultation. The heart was within normal limits. The abdomen was flat. There was no spasm or tenderness to palpation. The liver and spleen were not palpable. Rectal examination was not remarkable. Examination of the extremities revealed about nodules of approximately 0.6 cm in diameter in the extensor tendons of both hands and in the 1st and 5th toes. There was bilateral involvement of the Achilles tendons revealing 1.5 cm nodules unattached to the skin. There was no ankle edema. Arterial pulsations were present in both feet. Yellow-orange masses, approximately 3 cm in diameter, were noted in both elbows. In the knees, nodules of 4 cm in diameter were noted. All were movable, firm and nontender. There was no pigmentation in the skin. Neurological examination was negative except for the disturbance of left acoustic nerve. Temperature, pulse and respiration were normal. Blood pressure was 140/80 mmHg in the right arm.

Hematologic studies were negative. Urine sediments contained innumerable red cells per high-power field. The total serum proteins was 7.8 g/100 ml with an albumin of 4.6 g. Blood urea nitrogen was 6 mg, uric acid 7.9 mg, amylase 85U, lipase 14 IU, trypsin 890 ng. LCAT was not measurable because maximum was exceeded. Total serum cholesterol was 718 mg, and free cholesterol 236 mg (33 percent of the total), and triglycerides 173 mg/100 ml. Cholesterol distribution values in the lipoprotein fraction were as follows: α-lipoprotein-21%, pre- β-0%, β-78%, and chylomicron-1%. Measurement of the lipoprotein fraction revealed the following values: chylomicron-11 mg, very low density lipoprotein (VLDL)-211 mg, low density lipoprotein (LDL)-2488 mg, and high density lipoprotein (HDL)-16mg/100 ml. An insufficiency to tolerance of glucose was detected.

Stage I hypertensive retinopathy (Keith-Wagener classification) was evident. Electrocardiograms showed prominent negative T waves in leads V4 V5 V6 and ST-depression in leads V3 and V4.

Roentgenologic examination of the chest and abdomen were normal. Radiographic examination of the skull showed an extensive destructive process including the external and middle ear and lateral portions of the petrous ridge (Fig. 2a). The destruction extended anteriorly to the temporal bone and posteriorly to the inferior portion of the parietal and occipital bones over an area about 12 cm in diameter. Concurrently conducted computerized axial tomography of the head more clearly revealed the area of the radiolucency (Fig. 2b). Additionally, MRI-CT of the head further delineated the radiopaque area of the tumor (Fig. 2c).

At operation the area of bony destruction was found to consist of yellow-brown amorphous material, granulation tissue and bone spicules. Microscopical examination revealed a foreign body granuloma surrounding cholesterol deposits consisting of lipid histiocytes, giant cells and fibrocytic proliferation. The lesion extended into the surrounding bone. In addition, long needle-like crystalline clusters, which were birefringent under polarized light, were seen (Fig. 3a, 3b).

When seen, the patient was on a low-fat, low-calorie diet and was taking cholestyramine and lovastatin (inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA]). Total serum cholesterol was 558 mg per 100 ml, down approximately 22% pre-medication levels. Anginal attack was the presenting cause of the patient's admittance.

**DISCUSSION**

Gartmann first reported adult xanthogranuloma (AXG) in 1963 (1). Juvenile xanthogranuloma (JXG) had been described in 1954 by Helwig and Hackney (3). Many additional case reports of JXG have appeared (4–8) but only 30 cases of AXG have been reported in our country (7, 9–11). There is wide variation in age at onset, in distribution, size and duration of skin lesions. They most often make their appearance between the ages of 20
AXG with Familial Hypercholesterolemia

Table 1.

Family tree

Fig. 1. The elevation of the occipital bones is revealed.

Fig. 2a. The destruction extends anteriorly to the temporal bone and posteriorly to the inferior portion of the parietal and occipital bones.

Fig. 2b. Computerized tomography of the head clearly reveals the area of the tumor.

Fig. 2c. MRI-CT delineates the radio-opaque area of the same one.

Fig. 3a. Fibrocytic proliferation extend into the surrounding bone.

Fig. 3b. Giant cells, lipid histiocytes and long needle-like crystalline clusters are clearly seen.
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and 30 years. There may be single or multiple lesions with a single lesion being more prevalent in AXG than in JXG.

The head and neck are the most common sites. Size of the individual lesions vary from miliary-sized to soy bean sized. They are usually circular, slightly raised, smooth, and yellow to reddish-brown in color (12). The disease appears to be benign and usually undergoes spontaneous regression in one to four years. The incidence is equal between men and women. The disease does not seem to be familial and blood lipid studies are usually normal.

Histologically, the lesions contain histiocytes, foam cells, fibroblasts and Touton giant cells. Some of the histiocytes contain foamy cytoplasm (12). Fat stains usually reveal sudanophilic anisotropic lipoidal material throughout the lesion. Occasionally a mild inflammatory reaction is present.

Pathogenesis of AXG is unknown. Most investigators now believe the disease to be granulomatous rather than neoplastic.

Earlier workers had related the condition to xanthoma, xanthoma disseminatum, reticulohistiocytoma, and histiocytosis (including Hand-Schuller-Christian disease) (13-16). These diseases, which fall within the category xanthomatoses, have been divided into two groups, depending on the serum cholesterol concentration.

The first group which exhibits a high cholesterol is thought to result from an imbalance of cholesterol production and deposition. Secondary to the hypercholesterolemia there may be a deposition of cholesterol in the skin, tendons, blood vessels and reticuloendothelial system. Secondary xanthomatosis due to hyperlipemia, is also included into this group. An increase in neutral-fat concentration, which always accompanies hypercholesterolemia, is found in the serum. The mechanism is thought to be a fault in the transportation and/or deposition of neutral fat.

The second group has a normal cholesterol concentration and includes xanthoma disseminatum, histiocytosis, and reticulohistiocytoma. These diseases are neoplastic rather than granulomatous. Basically, histiocytes proliferate reactively and lipid is accumulated as a secondary phenomenon. As the disease progresses, lipidization of histiocytes increases with xanthoma-cell formation (13).

Xanthoma disseminatum is distinguished from AXG in the distribution of lesions in the extremities, axillae and especially mucous membranes. Histologically, however, this distinction may be impossible to make at all times (13). In reticulohistiocytoma, the cytoplasm of giant cells include hyalin structures and foam cells are only rarely seen. Histiocytosis is a systemic disease which invades bone marrow and cuts. It is easy to distinguish histiocytosis from AXG because of the difference in clinical course and histology.

In this case, because of family history and laboratory findings of high serum lipid content and cholesterol levels, a diagnosis of familial hypercholesterolemia-type IIa (WHO classification) is easily made. The skin lesions and the tendon involvement can be best classified as belonging to the group of essential xanthomatoses of hypercholesterolemic type referred to as “Xanthoma tuberosum and tendon xanthoma”.

The osteolytic skull lesion is roentgenologically and pathologically characteristic of lipid granuloma which resembles histiocytosis, especially Hand-Schüller-Christian disease. This disease has been classified as a normocholesterolemic xanthomatosis.

When the clinical and laboratory findings in this case are summarized, the following characteristics emerge, viz that the skull lesion is histologically typical of histiocytosis-like xanthogranuloma but hypercholesterolemia and xanthomas exist.

Only one case report was found in the literature that bore a resemblance to the case described above. Koch and Lewis reported hyperlipemic xanthomatosis with osseous lesion of the skull in 1956 (2). That case resembles this one in that an extremely rare occurrence of xanthogranuloma located in the skull was accompanied by hypercholesterolemia. In the report of Koch et al the etiology of the hypercholesterolemia was not ascribed to a familial condition.

In these two cases, it is thought that the bone lesions were a secondary involvement to the hypercholesterolemic xanthomatosis. We would like to suggest that a new syndrome emerges that has characteristics common to primary xanthomatoses, entities which are held to be etiologically distinct.
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**SUMMARY**

A case of adult xanthogranulomatous intracranial lesion associated with familial hypercholesterolemia is reported in detail.

**REFERENCES**