Coexistence of juvenile xanthogranuloma and diffuse plane xanthoma in 22-month-old boy could potentially be caused by digenic inheritance of *APOB* and *APOE4* polymorphism

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ABSTRACT:

SUNANTAWANICH K*, BOONPUEN N*, DENSUPSOONTORN N, VIPRAKASIT V**, TANTANASRIGUL P*, SUDTIKOONASETH P*, WESSAGOWIT V*. COEXISTENCE OF JUVENILE XANTHOGRANULOMA AND DIFFUSE PLANE XANTHOMA IN 22-MONTH-OLD BOY COULD POTENTIALLY BE CAUSED BY DIGENIC INHERITANCE OF *APOB* AND *APOE4* POLYMORPHISM. THAI J DERMATOL 2020; 36: 25-30.**

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The coexistence of juvenile xanthogranuloma and diffuse plane xanthoma is considered a rare phenomenon. We report a 22-month-old boy with multiple orange-tan papules and yellow plaques on his entire body for 18 months. Two types of histological findings confirmed the diagnosis of juvenile xanthogranuloma and plane xanthoma, respectively. Additionally, the patient's blood test showed high cholesterol level, which could be associated with familial or secondary dyslipidemia.

Key words: Juvenile xanthogranuloma, diffuse plane xanthoma, pediatric, dyslipidemia

Introduction

Juvenile xanthogranuloma (JXG) is the most common form of non-Langerhans cell histiocytosis. It usually presents with dome-shaped, yellow to erythematous papules or nodules which are often seen within the first year of life[1,2]. Diffuse plane xanthoma (DPX) is characterized by yellowish-orange plaques that often appear in the periorbital region, neck, upper trunk and flexural folds. DPX is an uncommon condition in children. Infantile-onset JXG coexisting with diffuse plane xanthoma is considered to be a rare phenomenon[3]. This is the second case after Le Birde *et al* who reported coexistence of xanthelasma and juvenile xanthogranuloma in a 7-year-old boy who had a past history of myelogenous leukemia[4].

Case report

A 22-month-old Thai boy with homozygous hemoglobin E disease presented with multiple orange-tan and yellow plaques on his entire body. At the age of 4 months, his parents noticed lesions on his face. The lesions had gradually increased in size and number. He denied history of taking any medications. No family medical history of any significant diseases.

Physical examination revealed two morphologies of skin lesions. First, generalized well-demarcated tan-orange papules were visible on the face, trunk and extremities; second, diffused well-defined yellowish plaques were found on the eyelids, periorbital areas, face, chest and back (Fig. 1 and 2). The remainder of the examination revealed no other abnormalities. Ophthalmic examination was normal. His weight was 12 kg. (50^{th} percentile) and height was 86 cm. (50^{th} percentile).

Laboratory tests showed the following results: hemoglobin 12.1 g/dL, white blood cell count 10,400 cell/mm^3, platelet count 496,000/mm3, cholesterol 190 mg/dL (acceptable: < 170), triglyceride 148 mg/dL (acceptable: < 75), high-density lipoprotein (HDL) 47 mg/dL (acceptable: ≥ 40), low-density lipoprotein (LDL) 123 mg/dL (acceptable: < 110)[5].

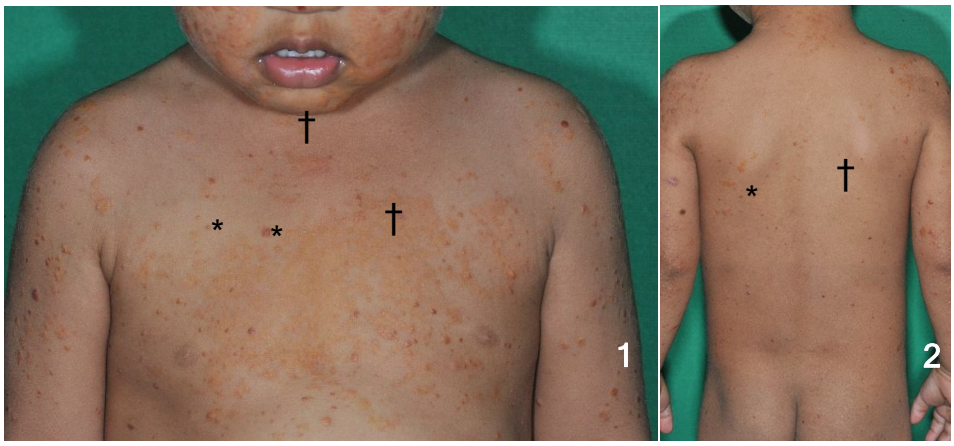

Figure 1, 2 generalized well-demarcated tan-orange papules (asterisk, *) and yellowish plaques (obelisk, †) on the face, trunk and extremities

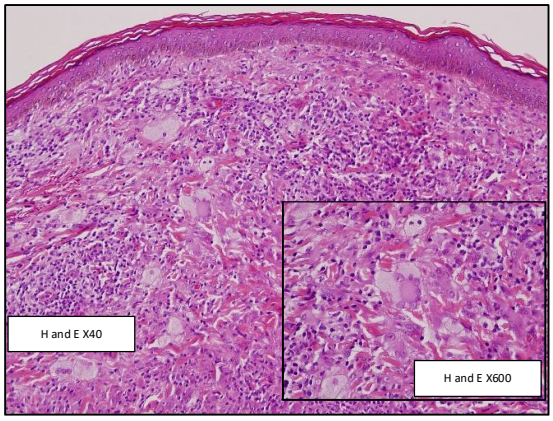

Figure 3 Focal aggregation of foamy histiocytes in upper dermis with Touton giant cell (inset)

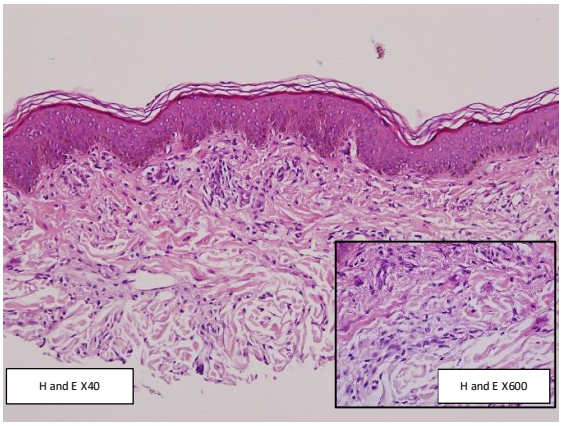

Figure 4 Diffused foamy histiocytes (inset) in the upper dermis

Histologic examination of a tan-orange papule on the left upper arm showed Touton giant cells with focal aggregation of foamy histiocytes in upper dermis, which confirmed the diagnosis of JXG (Fig. 3). Additionally, histologic findings of a yellowish plaque on the chest wall revealed diffused foamy histiocytes within the upper dermis. The overlying epidermis appeared unremarkable, which was consistent with xanthoma (Fig. 4).

Discussion

Juvenile xanthogranuloma (JXG) is a benign, self-healing disorder characterized by solitary or multiple yellow-red nodules on the skin and, occasionally in other organs. Most of JXG patients have a single lesion but multiple lesions are more

frequent in children younger than 6-month-old[6]. Additionally, extracutaneous JXG lesions have been reported in many organs. The eye, especially the iris, is the most frequent extracutaneous site which is usually seen in patients younger than 2-year-old with multiple JXG[7]. Other less common locations of JXG are the lungs, heart, central nervous system, pituitary gland, gastrointestinal system, kidney, adrenal gland, bones and bone marrow[1,6,8,9]. The pathogenesis of JXG is still unclear, but is thought to be secondary to a reactive proliferation of histiocytes following triggers such as physical trauma and viral infection as cytomegalovirus and varicella[6,7]. JXG has also been associated with neurofibromatosis type 1 (NF1) and juvenile myelomonocytic leukemia (JMML). A previous study from whole exome sequencing (WES) can identified the somatic mutations in *MAP2K1* (27% of the cases), *KRAS* (18%) and *NRAS* (18%) in twelve patients with JXG[18]. There is also a recent case report of a mitogen-activated protein kinase (MAPK) pathway mutation in *MAPK1* gene in one patient with disseminated JXG. Mostly, JXG without systemic involvement has a favorable prognosis. Spontaneous regression usually occurs within months to years. Surgical excision is occasionally performed for cosmetic concerns.

Plane xanthomas are the condition resulting from abnormal lipid deposition and foam cells in the skin which often associated with familial or secondary dyslipidemia. Among familial dyslipidemia, autosomal dominant hypercholesterolemia (type IIA) is relatively common. This group consists of familial hypercholesterolemia (FH) caused by the mutation of low-density lipoprotein receptor (*LDLR)* gene, familial defective apolipoprotein B-100 (FDB) with mutation in the Apolipoprotein B (*APOB*) gene, and non-FH/non-FDB hypercholesterolemia with mutations in the proprotein convertase subtilisin/kexin type 9 (*PCKS9*) gene[13]. This condition can be presented with diffuse cutaneous lesions all over the periorbital regions, neck, upper trunk and flexural folds, which was called diffuse plane xanthoma. Diffuse plane xanthoma is usually found in adults aged between 40 to 60 years[3], but it is rarely found in children. To the best of our knowledge, there are only two case reports of pediatric patients who have diffuse plane xanthomas without dyslipidemia[14, 15]. This condition has been associated with systemic diseases, particularly multiple myeloma and monoclonal gammopathy[15]. In the patient with limited involvement, there are many treatment modalities for removing plane xanthoma such as excision, chemical ablation, dermabrasion, and ablative laser therapy[17].

For this patient's dyslipidemia, we initially advised the patient to make dietary changes without prescribing any lipid-lowering medication.

We also found mild hypercholesterolemia (total cholesterol 229 mg/dl) in his mother who aged 28 years without xanthoma. At 6-, 18-, 24-month visits, the blood tests revealed hypercholesterolemia, high LDL but normal triglyceride levels. After 3 years of follow-up consultations, multiple orange-tan papules on the face disappeared; however, yellowish plaques on the eyelids, the face, and the chest were persistent.

We think that the patient's dietary might not be the only factor affecting his high lipid level; thus, we performed molecular genetic testing for the three known associated gene with familial heterozygous hypercholesterolemia, *APOB, LDLR* and *PCSK9*. Based on WES, we found no significant pathogenic mutations on *LDLR* and *PCKS9* genes but it showed that this patient was most likely affected by dyslipidemia due to digenic inheritance of *APOB*, C.293>T; p.Thr98Ile and *ApoE* polymorphism. No mutation of *APOB* was found in his parents.

Conclusions

We described a boy presented with JXG and DPX at the infancy-onset, which was considered a rare phenomenon. The diagnosis of JXG and DPX is mainly based on clinical characteristics and skin biopsy. This patient had dyslipidemia most likely due to digenic inheritance of *APOB*, c.293C>T;p.Thr98Ile and *APOE4* polymorphism. Although JXG and DPX are usually not related with dyslipidemia, investigation of lipid profiles should be kept in mind as possible comorbidity. However, the clinical onset of the systemic illness may be delayed in respect to the skin disease. All patients with diffuse plane xanthoma should obtain regular follow-ups to look for evidence of hematologic malignancy and abnormal lipid profiles.

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