β -Sitosterolemia with Generalized Eruptive Xanthomatosis

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Abstract. The clinical features of the first case of a patient with sitosterolemia and generalized eruptive xanthomatosis are described. A six-year-old girl with generalized eruption was referred to the lipid clinic because of the high plasma cholesterol levels determined by the enzymatic method. Neither clinical signs nor results of laboratory examinations appeared to be abnormal, except for the eruption and the increase in the plasma cholesterol concentration. A family survey revealed high plasma cholesterol concentrations in the mother and one of two other siblings. Histological examination showed the eruption to be a xanthoma. Plasma sterol analysis by high-performance liquid chromatography revealed a noticeable increase in plasma plant sterol as well as cholestanol concentrations in the proband and the hypercholesterolemic sibling. The other family members had slightly high plasma sterol concentrations. This is the first case of a sitosterolemic patient with eruptive xanthomatosis. The case indicates that the clinical features of the xanthoma in sitosterolemia are not only tuberous or tendon but also eruptive, and also suggests that sitosterolemia should be considered in the differential diagnosis of hypercholesterolemia in almost every case with tuberous or eruptive xanthoma. The diagnosis is clinically important, since the disease can be treated successfully by diet therapy and bile acid binding resins.

Key words: β -Sitosterolemia, Eruptive xanthoma, Tuberous xanthoma, Hyperlipidemia, Familial
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SITOSTEROLEMIA is a rare inherited disorder of lipid metabolism, and has been reported to show many clinical symptoms and signs such as multiple xanthomas of tendon and subcutaneous tissues, premature atherosclerosis, intravascular hemolytic anemia, splenomegaly, and platelet abnormality, and others [1]. One of the significant signs is xanthomatosis, and xanthoma has been reported to be tuberous or tendon. Previously we reported a very rare case of the disease showing signs of multiple spinal xanthomas which had induced neurological symptoms and signs due to

compression of the spinal cord [2, 3]. We encountered and report here the first case of sitosterolemia with generalized eruptive xanthomatosis.

Case Report and Family Study

A six-year-old girl was referred to our lipid clinic because of generalized xanthomatosis with high serum cholesterol levels. She had had localized eruption on both shoulders and forearms since the age of 4 years, and the eruptions had become general at the age of 5 years. The eruptions were yellowish and approximately 1 mm in diameter. She had been treated as having atopic dermatitis with steroid ointments. No clinical improvements, however, were observed with these treatments. She

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Fig. 1. Xanthomas of the sitosterolemic patients. a, Eruptive xanthoma in the back of proband; b, Eruptive xanthoma in the thigh of proband; c, Tuberous xanthoma in the first toe of sister (subject 4).

has had no arthralgia. Laboratory examination revealed a noticeable increase in serum lipid, total cholesterol 500 mg/dl and triglycerides 250 mg/dl after breakfast. There was no family history of sudden death or premature atherosclerosis, but one of the siblings (elder sister) had tuberous xanthoma in the hands, feet and buttocks.

The patient's height was 108 cm, and weight 18 kg. No physical abnormalities except for eruptive xanthoma (Fig. 1a, b) were observed. Neither tuberous xanthoma nor thickening of the Achilles' tendon were seen. Laboratory examination revealed moderate hypercholesterolemia as determined by the enzymatic method, but no other major abnormal findings including urinalysis, thyroid function tests (serum levels of TSH and free T4), and serum creatinine and fasting plasma glucose levels. Serum lipid levels of her family members at fasting are summarized in Table 1. Subject 2 (the mother) presented moderate hypertriglyceridemia, but serum triglyceride levels were only mildly increased in subjects 4 and 5.

Neither anemia nor thrombocytopenia was observed in any family member studied. Histological diagnosis of the eruption (subject 5) and tuberous tumor of the skin (subject 4) was xanthoma of the skin (Fig. 2).

Plasma sterol analysis was performed as described by Kasama *et al.* [4]. Plasma levels of plant sterols as well as cholestanol were noticeably increase in subjects 4 and 5 (Fig. 3), and a diagnosis of sitosterolemia was made. The plasma concentrations of sterols are shown in Table 2. A mild increase in plasma concentrations of plant sterols as well as cholestanol was observed in the mother and father (subjects 1 and 2) who should be obligatory heterozygotes of the disease as well as the brother (subject 3).

After establishing the diagnosis of sitosterolemia, a low cholesterol and low plant sterol diet was prescribed for the patient as well as the affected sibling. Diet therapy successfully decreased the plasma levels of plant sterols as well as cholesterol (Table 3). Serum triglyceride levels in both subjects

Table 1. Serum lipid levels in family members of sitosterolemic patient with eruptive xanthomatosis

Subject		Age (yrs)	Sex	Serum lipid levels at fasting			Apo E phenotype
				Total cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL cholesterol (mg/dl)	
1	Father	36	M	220	78	59	N.E.
2	Mother	34	F	230	535	28	E2/3
3	Brother	10	M	176	162	32	E3/3
4	Sister	8	F	431	195	24	E2/3
5	Proband	6	F	260	150	36	E3/3

N.E., not examined.

Fig. 2. Microscopic view of the xanthoma of the skin. a, At tuberosus tumor of buttock in subject 4, foamy cells had accumulated around perivascular spaces. b, At the eruptive sites in subject 5, small aggregations of foamy phagocytes were observed in the papillary dermis, i.e., just beneath the epidermal layer (Hematoxylin and eosin, $\times 200$).

decreased slightly after the treatment (195 mg/dl to 165 mg/dl in subject 4, 150 mg/dl to 112 mg/dl in subject 5). The sterol levels of plasma lipoprotein fractions separated by the ultracentrifugation method [5] in the two sitosterolemic subjects after diet therapy for 4 months are also summarized in Table 3. The sterol compositions of lipoproteins were similar in all lipoprotein fractions, in contrast to the original report [6] which described the predominant distribution of plant sterols in low density lipoprotein fraction. The xanthomas (tuberosus in subject 4, and eruptive in subject 5) diminished in size during the diet therapy, and eruptive xanthoma in the face in subject 5 as well as tuberosus xanthoma on the plantar side of proximal end of the first toe (Fig. 1c) disappeared almost completely.

Discussion

Xanthomatosis is an important clinical sign in familial hyperlipidemic diseases. Tuberosus and tendon xanthomatosis is characteristic of hypercholesterolemic diseases such as familial hypercholesterolemia [7]. Eruptive xanthomatosis, on the other hand, is characteristic of moderate or severe hypertriglyceridemic hyperlipidemia such as type I, III and V hyperlipidemia in the WHO classification.

Sitosterolemia is a rare inherited disease in which plant sterols are accumulated in the whole body. Since the first report of two cases of the disease [6], 31 patients from 20 families have been described in the literature [1, 8–11]. Clinical

Fig. 3. Elution pattern of benzoate derivatives of plasma sterols in siblings of subject with sitosterolemia and generalized eruptive xanthomatosis. Left, subject 3 (brother); middle, subject 4 (sister); right, subject 5 (proband). Peak 1, desmosterol (internal standard); peak 2, cholesterol; peak 3, campesterol; peak 4, cholestanol; peak 5, sitosterol.

Table 2. Plasma sterol concentrations in family members of a sitosterolemic patient with eruptive xanthomatosis determined by HPLC (mg/dl)

Subject	Cholesterol	Sitosterol	Campesterol	Cholestanol
1	195	0.9	1.1	0.6
2	225	0.9	1.5	0.9
3	159	2.2	1.4	0.6
4	388	25.3	20.1	6.5
5	233	18.6	14.6	3.1
Control (n=15)	236 ± 38	1.05 ± 0.26	0.74 ± 0.36	0.43 ± 0.12
Range	193–323	0.78–1.73	0.24–1.7	0.20–0.76
Normal (n=10)	187 ± 25	0.71 ± 0.13	0.48 ± 0.23	0.39 ± 0.18
Range	140–240	0.51–0.99	0.20–0.87	0.10–0.79

The sterol levels were determined after derivatization of extracted nonsaponifiable fractions of plasma with desmosterol as an internal standard. Normal values were obtained from healthy subjects, and control values from hyperlipidemic subjects without xanthoma. The values are the mean ± SD.

presentation includes xanthomas, premature atherosclerosis, hemolysis, thrombocytopenia, splenomegaly, and arthralgia [12]. Tuberous or tendon xanthoma has been reported as a characteristic feature of the disease as seen in subject 4 in this family, but no case of eruptive xanthomas has previously been reported. The case presented here is the first reported incidence of

sitosterolemia with generalized eruptive xanthomatosis. Eruptive xanthomatosis has been reported to be associated with severe hypertriglyceridemia such as chylomicronemia syndrome including familial lipoprotein lipase deficiency, in which serum triglyceride levels are more than 2,000 mg/dl [13]. It is therefore difficult to speculate on the etiology of the eruptive

Table 3. Sterol concentrations after dietary treatment in plasma lipoprotein fractions of two sitosterolemic patients determined by the HPLC

	Before treatment	After 4 month of diet therapy				
	Plasma	Plasma	VLDL	IDL	LDL	HDL
Subject 4						
Cholesterol	388	173	17.5	11.5	111	24.9
Sitosterol	25.3	12.2	0.8	0.8	8.9	2.1
Campesterol	20.1	9.6	0.8	0.6	6.9	1.4
Cholestanol	6.5	2.6	0.2	0.2	1.9	0.3
Subject 5						
Cholesterol	233	191	8.5	8.0	144	30.8
Sitosterol	18.6	14.2	0.4	0.5	10.6	2.7
Campesterol	14.6	11.6	0.4	0.5	8.7	2.0
Cholestanol	3.1	2.5	0.1	0.1	1.9	0.4

Samples were taken at fasting after low-cholesterol and low-plant sterol diet therapy for 4 months.

xanthoma in this case since serum lipid levels were only mildly hypertriglyceridemic (less than 300 mg/dl even after meals). Although we could not determine the sterol composition of the eruptive and tuberous xanthoma in this family because of the difficulty of obtaining the consent to re-biopsy the xanthomas, the eruptive xanthoma persisted for more than one year without significant fasting hypertriglyceridemia. The xanthomatosis may therefore be attributable to the inherited sitosterolemia, even though this unique clinical sign should in future be confirmed in other cases of this rare disease by not only histological examination but also a chemical composition study. Questions also remain as different types of xanthoma were observed in the same family of sitosterolemia (eruptive in subject 5 and tuberous in subject 4). It is possible that other congenital or environmental factors may contribute to the pathogenesis of eruptive xanthoma, since the mother of the proband had hypertriglyceridemia as well as mild hypercholesterolemia, as shown in Table 1.

It has been reported that a low plant sterol diet improves the clinical symptoms and signs of sitosterolemia especially xanthomas in young patients [9, 14]. In the subjects presented here,

xanthoma as well as plasma lipid levels were improved by diet therapy. We have reported three middle-aged patients with sitosterolemia apart from this family [14]. The tuberous and tendon xanthoma of three patients were not clinically improved despite the successful reduction of plasma sterol concentrations by diet and cholestyramine therapy for more than five years. It is therefore important that the lipid abnormalities be treated at a young age to prevent not only the persistence of the xanthoma but also the progression of premature atherosclerosis in sitosterolemia.

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