Perineural Xanthoma Associated With Type 2 Diabetes Mellitus and Hyperlipidemia

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Practice Points

- Perineural xanthoma is a painful tumor.
- Perineural xanthoma is one of the skin manifestations (dermadromes) of diabetes mellitus and hyperlipidemia.
- Perineural xanthoma may become a hint of diabetic neuropathy.

It is well known that patients with diabetes mellitus (DM) may demonstrate skin manifestations, or dermadromes, due to disease-related metabolic, vascular, neurologic, and/or immunologic disturbances; however, the pathogenesis of some of these manifestations remains unknown. Xanthomas often are associated with increased levels of serum cholesterol and/or triglycerides and therefore can present as a dermadrome in patients with a history of uncontrolled DM and hyperlipidemia. The presence of tender lesions in this patient population can indicate a diagnosis of perineural xanthoma. We report a case of perineural xanthoma arising in a patient with type 2 DM and hyperlipidemia.

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It is well known that patients with diabetes mellitus (DM) may demonstrate skin manifestations due to disease-related metabolic, vascular, neurologic, and/or immunologic disturbances; however, the pathogenesis of some of these manifestations remains unknown.[1] The term *perineural xanthoma* was coined by Nakayama et al[2] who reported a case of xanthoma characterized by a concentric multilayered accumulation of xanthoma cells around peripheral nerve fibers in the dermis. In this case, the lesion presented as painful reddish plaques on the soles of the feet in a patient with a history of hyperlipidemia associated with type 2 DM.[2] We report a similar case of perineural xanthoma arising in a patient with hyperlipidemia and type 2 DM.

Case Report

A 58-year-old man with a history of hypertension and type 2 DM reported upper back pain while undergoing inpatient treatment of nephrotic syndrome. He indicated having an unpleasant sensation in the upper back followed by occasional pain for 2 months. He had been diagnosed with type 2 DM 26 years prior, which had been treated with insulin (46 U/d) for the last 4 years. He also had a 1-year history of nephrotic syndrome. There was no family history of lipid abnormalities or consanguineous marriage. In addition to insulin therapy, the patient's current medications included aspirin (100 mg/d),

digoxin (0.125 mg/d), and furosemide on a symptomatic basis.

Physical examination of the upper back revealed 4 red nodules (approximately 3 cm in diameter) that were firm, oval shaped, and tender (Figure 1). The differential diagnoses included erythema nodosum, ganglion, and neuritis due to DM. Laboratory test results revealed a fasting blood glucose level of 108 mg/dL (reference range, 60–110 mg/dL) and a glycosylated hemoglobin value of 6.5% (reference range, 4.7%–6.2%). Total cholesterol was 456 mg/dL (reference range, 130–220 mg/dL) at presentation, and triglycerides ranged from 1273 to 2468 mg/dL (reference range, 30–150 mg/dL) in the 3 months prior to presentation despite treatment with ethyl icosapentate (1800 mg/d). Other laboratory test results are shown in the Table. An abdominal ultrasound revealed no enlargement of the pancreas or spleen, but evidence of chronic liver damage was noted.

Histologic examination of a biopsy specimen taken from one of the nodules showed an accumulation of foam cells around the nerve fibers in the dermis (Figures 2A and 2B). Dermal vessels were slightly dilated and a chronic inflammatory infiltrate was noted. The foam cells were arranged around the peripheral nerves. Closer examination revealed that the foam cells were located in the perineural space (Figure 2C). The epidermis was not involved. Ziel-Neelsen staining for acid-fast bacilli was negative. We made the diagnosis of perineural xanthoma based on the histologic findings of a prior report.[2]

Intensive insulin therapy and supportive care were administered. The patient was advised to consume a diet low in saturated fats and cholesterol. Although the peak dose of insulin was 46 U daily, the dosage was reduced to 6 U daily due to kidney function deterioration. One month following diagnosis, laboratory testing showed an improved lipid profile (Table). Two months later the patient's nodules had decreased in size and there was no tenderness. Three months later hemodialysis was initiated for treatment of refractory edema. After 10 months the nodules had completely resolved.

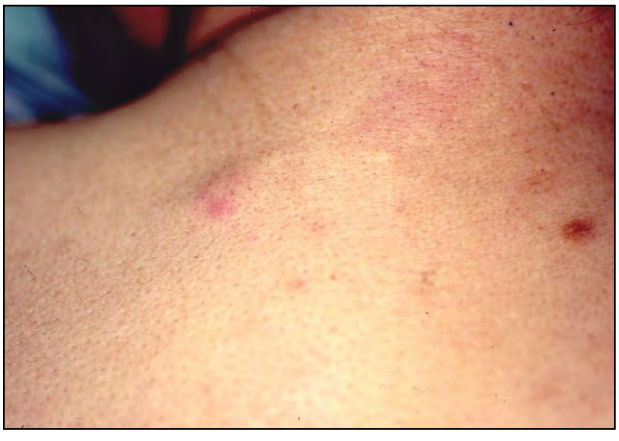

Figure 1. Tender nodules on the left side of the upper back.

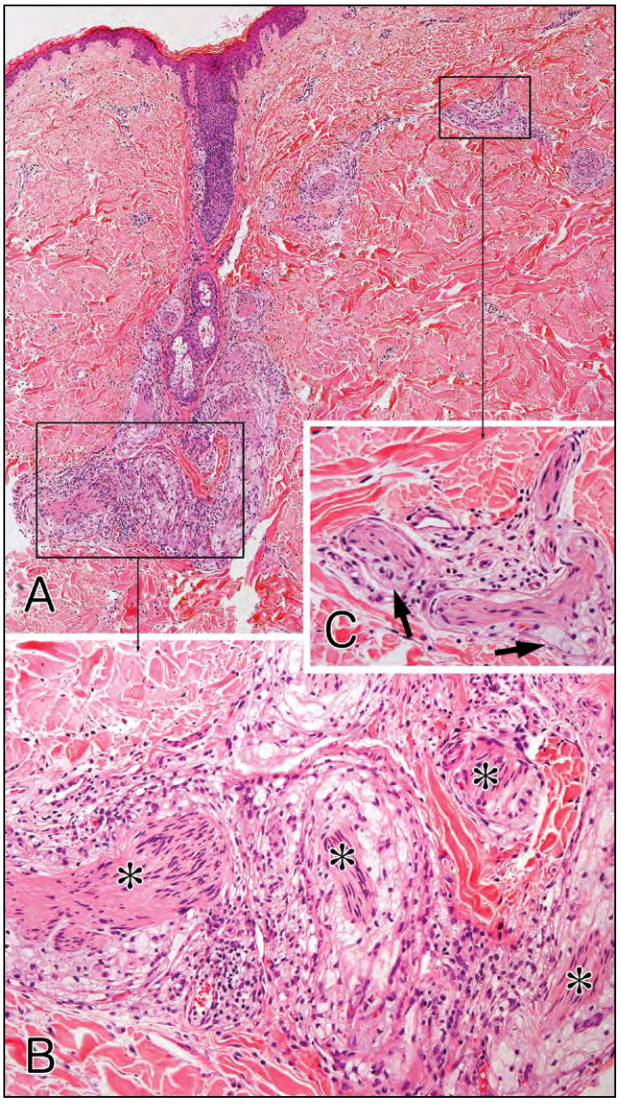

Figure 2. Histopathologic examination of a skin biopsy specimen taken from one of the nodules revealed an aggregation of xanthomatous cells around the peripheral nerve fibers in the dermis (A)(H&E, original magnification ×100). An infiltrate of inflammatory cells and capillary dilation also was observed. Higher magnification showed nerve fibers (asterisks) surrounded by a xanthomatous infiltrate (B)(H&E, original magnification ×400). Foam cells were located between the nerve fibers and the perineurium (arrows)(C)(H&E, original magnification ×400).

Laboratory Test Results[a]

Laboratory Parameters (Unit of Measure)	Reference Range[b]	3 Mo Before Presentation	2 Mo Before Presentation	1 Mo Before Presentation	At Presentation[c]	1 Mo After Presentation	2 Mo After Presentation	3 Mo After Presentation
Creatinine (mg/dL)	0.6–1.1	1.9	2.4	2.5	2.7	3.0	3.3	4.6
Cholesterol (mg/dL)								
Total cholesterol	130–220	N/A	N/A	N/A	456	N/A	N/A	N/A
High-density lipoprotein cholesterol	41–74	22	17	26	21	N/A	N/A	N/A
Low-density lipoprotein cholesterol	<140	93	91	118	85	104	143	164
Triglycerides (mg/dL)	30–150	2468	1403	1288	1273	1052	575	329
Total protein (g/dL)	6.5–8.0	4.7	4.4	4.6	N/A	4.0	N/A	6.0
Albumin (g/dL)	3.7–5.2	1.7	1.7	2.0	1.9	1.6	1.5	2.8
24-h urine collection								
Total volume (mL)	N/A	N/A	N/A	N/A	800	N/A	1700	N/A
Creatinine (mg/dL)	0.6–1.1	N/A	N/A	N/A	2.7	N/A	3.3	N/A
Total protein (mg/L)	30–120	N/A	N/A	N/A	1310.2	N/A	551.9	N/A
Timed creatinine (h)	82–140	N/A	N/A	N/A	18	N/A	20	N/A
Timed protein (mg/24 h)	N/A	N/A	N/A	N/A	10,481.6	N/A	9382.3	N/A

Abbreviation: N/A, not available.

[a]To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113.

[b]Reference values are affected by many variables (eg, patient population, laboratory methods used). The reference ranges used at Osaka Red Cross Hospital in Japan are for adults who are not pregnant and do not have medical conditions that could affect the results; therefore, these reference ranges may not be appropriate for all patients.

[c]At the time of referral to the dermatology department.

Comment

There are some similarities between our patient and the first case of perineural xanthoma reported by Nakayama et al.[2] Clinically, both patients were in their 50s and had a history of type 2 DM that had been treated with insulin; both also had hyperlipidemia and liver damage. In both cases, the lesions were erythematous and tender. Notably, a common histologic finding was the presence of foam cells, namely xanthoma cells, around the peripheral nerve fibers in the dermis. The xanthoma cells were located between the nerve fibers and the perineurium.

Xanthomas are associated with increased levels of serum cholesterol and/or triglycerides. The increased serum lipid levels cause tissue lipid infiltration, which are subsequently phagocytosed by dermal macrophages, in consequence forming xanthomatous lesions.[3,4] Peripheral nerves are isolated from blood constituents by the blood-nerve barrier, which is related to the blood-brain barrier. Bundles of nerve fibers are covered by multilayered perineural cells that are connected by tight junctions.[5,6] Therefore, xanthomas generally are not associated with tenderness and do not histologically demonstrate an accumulation of xanthoma cells around peripheral nerve fibers. The perineurium, which is the outermost layer of branched peripheral nerves in the dermis, extends distally with a sheath of capsular cells and functionally insulates external stretching forces.[7] We speculated that in our patient the xanthoma cells within the perineurium caused constriction of the nerve fibers due to the limited space in the perineurium, thereby causing tenderness in the perineural xanthoma lesions.

The incidence of perineural xanthoma appears to be rare considering the number of patients with hyperlipidemia associated with type 2 DM. The lesions seem to be related to a disturbance of lipid metabolism due to DM-associated insulin deficiency.[8] Our patient also demonstrated hepatic dysfunction, which promoted accumulation of lipids in the tissue and disturbed transportation of lipids in the serum.[9] The hepatic dysfunction may have exacerbated the increased levels of circulating cholesterol that manifested in the skin as perineural xanthoma. Obstructive jaundice, nephrotic syndrome, and DM may cause secondary hyperlipidemia. The nerve damage is thought to be caused by the leakage of lipoproteins.[10]

In our patient, tenderness of the lesions resolved after deterioration of renal function and aggravation of liver damage. Functional deterioration of these organs may have resulted in the reduction of triglyceride synthesis in the liver and reduced serum levels, which consequently diminished the tenderness of the lesions.

Skin disorders that appear in association with internal diseases are called dermadromes. Dermatologists should be aware of xanthoma as a common dermadrome associated with uncontrolled DM and hyperlipidemia.[1] The presence of tenderness may be characteristic of perineural xanthoma; therefore, perineural xanthoma should be considered as a dermadrome due to hyperlipidemia associated with DM.

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