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Adverse reactions of Achilles tendon xanthomas in three hypercholesterolemic patients after treatment intensification with niacin and bile acid sequestrants

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Abstract: Multiple cholesterol-reducing therapies have been shown to induce the regression of tendon xanthoma in patients with familial hypercholesterolemia. We present 3 cases of adverse reactions in Achilles tendon xanthomas after the addition of niacin and bile acid sequestrants to ongoing statin therapy. Reduction in tendon dimensions and marked softening of xanthomas were interpreted as cholesterol removal from heavily infiltrated tissue sites. In 2 cases, changes in the xanthomas occurred despite only minor lipoprotein improvements, raising the possibility of direct drug effects in cholesterol-infiltrated tissue. Intriguingly, recent studies have described niacin receptor-mediated effects in macrophages. In summary, although adverse reactions in Achilles tendon xanthomas appear to be infrequent, clinicians should be aware of this phenomenon in their patients after intensifying lipid treatments, especially with the use of niacin in patients with familial hypercholesterolemia. Xanthoma responses may provide clues to new pharmacologic effects in cholesterol-infiltrated tissues.

Tendon xanthomas in patients with familial hypercholesterolemia (FH) represent a natural model of cholesterol-infiltrated collagenous tissue. Tendon xanthomas are structurally and compositionally similar to the fibrous cap of atherosclerotic plaques, but xanthomas offer the advantage of accessibility for ongoing clinical observation.[1–7] Cholesterol deposition in the Achilles tendon leads to thickening and sometimes to inflammation and impairment of function.[8]

Regression of tendon xanthomas has been observed with multiple pharmacologic therapies, including statins, bile acid sequestrants, ezetimibe, and niacin.[9–11] A common mechanism of action for these agents is improvement of lipoprotein profiles.

Niacin may exert additional effects in cholesterol-infiltrated tissue via ligation of the nicotinic acid receptor (GPR109A) in tissue macrophages, potentially increasing reverse cholesterol transport and reducing progression or inducing regression of lesions.[12–14] We have favored the addition of niacin in FH because atherosclerotic lesion regression has been demonstrated repeatedly in human clinical trials with niacin-containing combination therapy.[15–18]

If lipid deposition is far advanced in a tissue, removal of the lipid might disrupt tissue architecture and stability, resulting in at least transient worsening of clinical status. We present 3 clinical cases suggestive of this concept.

Case descriptions

During a period of 19 years in an academic lipid clinic, 3 patients of 236 with FH exhibited clinical worsening of

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Achilles tendon xanthomas shortly after the addition of niacin with or without a bile acid sequestrant to their ongoing statin therapy (summarized in Table 1). Niacin therapy was initiated in a total of 130 FH patients.

Case 1

A 46-year-old man with FH presented with a 2-year history of medically managed angina pectoris. Physical examination revealed corneal arcus, metacarpal tendon xanthomas, and Achilles tendon xanthomas measuring approximately 2.5 cm. Extended-release niacin was added to atorvastatin. During the course of 6 months he developed Achilles tendon tenderness, and by 13 months he largely discontinued lipid-modifying medications because of tendon pain and difficulty performing his job in a machine shop, which required frequent squatting. With infrequent use of lipid medications, his level of low-density lipoprotein cholesterol increased and tendon pain improved. He was asked to resume atorvastatin and titrate extended-release niacin based on tolerance of the tendon pain. Within 2 months he again had mild tenderness of the Achilles tendons but felt that it was tolerable. Five years after initial presentation, he stopped lipid medications for a period of months because of relocation and developed accelerated angina requiring 3-vessel coronary bypass surgery. During the following 7 years, his coronary disease and Achilles tendons have been asymptomatic.

Case 2

A 41-year-old woman with FH had a history of stent placement at age 38 secondary to total left anterior descending artery occlusion. Previous statin therapy was limited by myalgias, but she tolerated rosuvastatin. She exercised daily. On examination, she had corneal arcus and Achilles tendon xanthomas measuring 3.2 cm (right) and 3.0 cm (left). Within 3 months of adding immediate-release niacin and colesevelam to rosuvastatin, she developed severe Achilles tendon pain and tenderness limiting her ability to exercise and necessitating a walker for ambulation. She continued to titrate up her niacin dose. By 10 months her pain had nearly resolved, and she resumed daily exercise activities. She was asymptomatic after 17 months of combination therapy. Her Achilles tendons measured 2.5 cm on the right and 2.6 cm on the left.

Case 3

A 64-year-old woman presented with FH, peripheral arterial disease, and recent coronary bypass surgery. On examination, she had corneal arcus, xanthelasma, and bilateral xanthomas of the Achilles tendons, metacarpal tendons, and fascial tissues lateral to the tibia. Immediate-release niacin and cholestyramine were added to rosuvastatin therapy. Within 1 month she required stenting of a vein graft for recurrent angina. At 2 months multiple xanthomas softened described as resembling "fatty tissue" on palpation. The right Achilles tendon xanthoma developed fluctuance at 5 months. At 8 months, a small amount of clear drainage was noted by the patient. This was followed by a coagulase negative staphylococcal infection in the right Achilles tendon, requiring surgical debridement and intravenous antibiotics. Lipid treatment was switched to ezetimibe and simvastatin. During the next 5 years, she required additional antibiotics, surgical debridement, and skin graft placement secondary to *Staphylococcus aureus* infections in the left Achilles tendon and a protuberant xanthoma of the fascial tissues lateral to the right tibia.

Discussion

The 3 cases illustrate infrequent adverse effects in stable tendon xanthomas after intensification of lipid therapy. Tendon inflammation was likely aggravated by physical strain in Cases 1 and 2. Nevertheless, tendon inflammation and pain stabilized or resolved after continued intensive combination lipid therapy in both patients, whereas tendon thickness decreased substantially in Case 2. Acute tendonitis and tenosynovitis has been described previously in untreated FH patients.[19] However, to our knowledge, tendonitis has not been described after treatment intensification.

Within months of initiating combination lipid treatment in Case 3, a palpable change of softening occurred in multiple xanthomas. Fluctuance in the region of the right Achilles tendon was thought to represent a seroma formed after disruption of lymphatics. This led to susceptibility to infection.

Tendon xanthomas contain large amounts of unesterified and esterified cholesterol interspersed among collagen fibrils, fibroblasts, and macrophage foam cells. Lipids comprise 33% tissue dry weight, more than collagen at 24%.[1] Total lipids have a varying composition with 10% to 50% unesterified cholesterol and 25% to 75% cholesteryl ester.[1,2] Unesterified cholesterol deposits are predominantly extracellular, whereas esterified cholesterol is localized within macrophage foam cells.[3] These conditions mirror the composition and histology of the fibrous cap of human atherosclerotic plaques.[4–7] Tendon xanthomas in FH are a marker of underlying ischemic heart disease, with thicker Achilles tendons noted in persons with coronary disease compared to persons without coronary disease.[20]

Although posttreatment measurement of Achilles tendon width was unavailable for Case 1, there was evidence of a change in size or physical characteristics of the tendon xanthomas in Cases 2 and 3. Given the large contribution of cholesterol and cholesteryl esters to tissue bulk in xanthomas, it seems reasonable to assume that reverse cholesterol transport occurred.

The lipoprotein profile improved substantially in Case 1 but changed only modestly in Cases 2 and 3 by the time adverse reactions in the Achilles tendons were noted within 6 months of first exposure to niacin. Rubic et al[12] reported that niacin stimulated transcription of CD36 and ATP-binding cassette protein-A1 and enhanced high-density lipoprotein–mediated cholesterol efflux in monocytoid cells. Recently,