Xanthomatosis in bilateral hands mimicking rheumatoid arthritis
A case report
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Abstract
Rationale: Xanthomatosis often accompanies familial hypercholesterolemia. This disease usually occurs in tendons, most commonly located in the Achilles tendon; occasionally it can also be seen in other systems. Although there are previous reports for bilateral hand extensor tendon involvement, to our knowledge there is no report in English literature regarding bilateral hands with small joint synovium presenting as rheumatoid arthritis. Therefore, the case that is presented in this report is unique.

Patient concerns: An 18-year-old woman was admitted to our department because she presented with morning stiffness, joint deformation, and swelling in both hands. Computed tomography of the right hand showed soft tissue swelling on multiple small joints, including metacarpophalangeal and proximal interphalangeal joints, but without obvious bone destruction. There was soft tissue swelling around the small joints, which were hypointensities on T1-weighted and hyperintensities on T2-weighted images, not uniformly enhanced appearances on magnetic resonance imaging.

Diagnoses: Biopsy from the 3rd metacarpophalangeal joint capsule of the left hand confirmed xanthoma.

Interventions: She was treated with statin drugs to reduce blood fat.

Outcomes: After 3 months of follow-up, no recurrence or complications were detected regarding a full range of motion remaining of the affected joints.

Lessons: The young patient with symptoms of small joint synovium involved in both hands and the performance of magnetic resonance imaging similar to rheumatoid arthritis may be suffering from xanthomatosis.

Abbreviations: Anti_ccp = anticyclic citrullinated peptide antibodies, ERA = early rheumatoid arthritis, LDLC = low-density lipoprotein cholesterol, MCP = metacarpophalangeal, MRI = magnetic resonance imaging, RA = rheumatoid arthritis, RF = rheumatoid factor.

Keywords: hand, magnetic resonance imaging, rheumatoid arthritis, xanthomatosis

1. Introduction
Xanthoma is a tumor-like lesion mainly manifesting as hyperlipidemia.[1] This disease usually occurs in tendons, among which the Achilles tendon is the most common location. Occasionally, it can also be seen in other systems, such as central nervous system, ocular system, cardiovascular system, respiratory system, enterohepatic system, presenting with corresponding clinical symptoms. At present, research shows that most patients have a family history of hypercholesterolemia. In addition, it has been acknowledged that the cerebrotendinous xanthomatosis, an autosomal recessive inherited disease, resulting from abnormal cholesterol deposition associated with mutations in the CYP27A1 gene encoding the sterol-27-hydroxylase.[1] However, this case involved bilateral hand small joint synovium, which presented similarly to rheumatoid arthritis (RA), and is therefore unique.

2. Case report
2.1. Patient information
An 18-year-old woman complained of swelling with morning stiffness in multiple small joints, including the metacarpophalangeal (MCP) and proximal interphalangeal of both hands, and the 1st metatarsophalangeal joint of the left foot, without pain, fever, or signs of Raynaud symptoms. In recent years, the swelling in the joints worsened and joint deformation occurred; in addition, an oval mass appeared on the lateral margin of the right foot. When she was 2 years old, she had multiple nodules on the elbow joint, popliteal fossa, and hip, without any inducements. After surgical resection, the lesion relapsed again symmetrically so that the patient underwent an open excisional biopsy bilaterally on the elbows, first web, heel, and popliteal fossa under general anesthesia in our hospital 3 years ago. After the retraction of the subcutaneous tissue, 4cm×4cm×4cm (the largest), solid, soft, sharply defined, yellowish masses were detected. A biopsy specimen showed juvenile xanthogranuloma (Fig. 1). Immunohistochemical staining revealed that CD68 (+), CK (−), Ki-67 (+), CD1a (−), S100 (−), and acid fast staining (−).
2.2. Clinical findings

Her routine laboratory examination showed that serum cholesterol and low-density lipoprotein cholesterol (LDLC) levels were above normal, and the levels of antistreptolysin O and anticyclic citrullinated peptide antibodies (Anti_ccp) were also higher than the normal range; but the levels of erythrocyte sedimentation rate, antinuclear antigen, human leukocyte antigen-B27, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibodies, complement, total protein, C-reactive protein, and blood glucose were normal.

Computed tomography of the right hand showed that there was only soft tissue swelling on multiple small joints, which revealed hypointensities on T1-weighted images and hyperintensities on T2-weighted images (Figs. 2 and 3). In additional, there was an interesting finding of an RA appearance, which was thickened, fusiform, and not uniformly enhanced (Fig. 4). Synovial hyperplasia or inflammation of the small joints was also observed.

Figure 1. Juvenile xanthogranuloma: microphotograph (H&E ×100) showing Touton giant cell-like nuclei, extracellular lipid, and foamy macrophages. H&E = hematoxylin and eosin.

Regarding our findings and the clinical progression, the patient underwent an open excisional biopsy and tenolysis of the 3rd MCP joint in her left hand. A biopsy specimen showed several foamy cells in fibrous and fat tumor-like hyperplasia (Fig. 5). Further, immunohistochemical staining revealed CD68 (+), S100 (−), MDM-2 (+), HHF (focal+), LCA (+), and Ki-67 (5%+). Finally, it was diagnosed as xanthoma. After 3 months of follow-up, no recurrence or complications were detected regarding a full range of motion remaining of the affected joints.

2.3. Diagnostic assessment

In this case, the patient was an 18-year-old woman with positive Anti_ccp and morning stiffness, which was easily misdiagnosed for RA, especially in the early stage. According to early rheumatoid arthritis (ERA) diagnostic criteria[3] (Table 1), the patient could be confirmed as ERA. However, RA is defined as a systemic disease of unknown etiology, manifesting as chronic, symmetric, polyarthritis. When there is inflammation, there should be pain. In this case, no joint pain was detected, which did not conform to the typical performance of RA. Taking laboratory examination results into consideration, the levels of total cholesterol and triglycerides were also above normal; it should also be considered that this disease related to whole body metabolic abnormalities or abnormal lipid deposition. It is imperative to evaluate the lesion with the biopsy, because the treatment principle of xanthoma is essentially different from the RA. For the xanthoma, the basic treatment principle is a balanced diet and reducing blood fat, namely, to strengthen health education, adjust the diet structure, restrict calories in food intake, give lipid-decreasing drugs regularly, and detect hematric fat on a regular basis. Moreover, xanthomas on different parts of the body should be treated accordingly. For example, nodular xanthoma on the Achilles tendon can be resected; however, eyelid xanthoma can be treated in steps by using freeze or laser surgery, etc.

2.4. Therapeutic intervention and follow-up

The patient was treated with 20mg of atorvastatin daily to reduce blood fat during her hospitalization. Her cholesterol and LDLC levels fell from 16.12 and 13.30mmol/L to 11.92 and 10.20mmol/L, respectively. After being discharged, she was
Figure 3. MRI-unenhanced scanning: T1-weighted image of right hand showing hypointense lesions (upper left), and T1-weighted image-fat showing lower intense than T1-weighted image (upper right). MRI T2-weighted image and Proton density-weighted image-fat saturation showing hyperintensities lesions (lower left and right). MRI = magnetic resonance imaging.

Figure 4. Magnetic resonance imaging-enhanced scanning: T1-weighted image contrast enhanced showing thickened, fusiform, and not uniformly enhanced lesions, mimicking “rheumatoid arthritis” appearance. Synovial hyperplasia or inflammation in small joints was also observed.
switched to 10 mg of rosuvastatin daily. However, during her regular 3-month follow-up, her lipid level effect was poorly controlled—the levels of cholesterol and LDLC were higher.

3. Discussion

Multiple nodule types of xanthoma are generally seen in the elbow, knee, hip, ankle and other extension surfaces of large joints, which are distributed symmetrically, including Achilles tendon. However, the case presented in this report is even more unique as symptoms were observed bilaterally with small joint synovium, and the performance of magnetic resonance imaging (MRI) and some clinical manifestations were similar to RA. Thus, it was easy to be misdiagnosed as RA.

Multiple xanthoma is very rare but is a distinct metabolic disease, characterized as lipid deposition secondary to proliferation of histolytic cells. Pathogenesis is mainly shown by the focal excessive production of plasma cholesterol and triglycerides accumulation in different tissues, such as tendons, the brain, joints, skin, etc. Therefore, according to the different involved sites and the form, respectively, named as flat xanthoma, eyelid xanthoma, nodular xanthoma, rash-like xanthoma, tendon xanthoma, palm xanthoma, and disseminated xanthomatosis. Flat xanthoma occurs in the upper eyelid; palm xanthoma shows in the metacarpus and the creased side of the palm; nodular xanthoma is found in the elbow, knee, hip, and ankle joints; tendon xanthoma occurs in tendon adhesion; disseminated xanthoma can be symmetric and occurs in the face, neck, and chest; rash-like xanthoma often appears suddenly in a batch, which are papule for all sizes. 

Xanthoma image findings may vary according to the lesion sites. First, a brain MRI revealed cerebellar atrophy, white matter signal alterations, T1-weighted and T2-weighted symmetric hyperintensities in the dentate nuclei; additionally, there was an interesting finding of a “hot cross bun” appearance in the pons on MRI T2-weighted axial images. Second, MRI results of both ankles showed fusiform thickening, long-T1-weighted and short-T2-weighted image with heterogeneous signals. Third, radiological images of the lesions in the lungs manifested as diffuse, nodular, infiltrated, and fibrotic shadows, which suggested interstitial pulmonary dysfunction or xanthomatous lesions.

4. Conclusion

The summary of clinical diagnosis of xanthoma are as follows: related to the clinical symptoms, such as progressive memory loss, epilepsy, and other neurological symptoms; specific clinical signs: skin lesions, bilateral Achilles tendon masses, which often are symmetric, etc.; laboratory tests: hyperlipidemia or hypercholesterolemia; and the imaging examination on different parts. However, the final diagnosis still depends on the pathological results.

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