Seropositive rheumatoid arthritis in a patient with familial hypercholesterolemia: case report and literature review

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Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by hypercholesterolemia and early onset atherosclerosis. It may be misdiagnosed as rheumatoid arthritis (RA) because of swelling in the joints and periarticular area and can mimic arthritis or rheumatoid nodules. This report presents the case of a patient with FH manifested by seropositive RA. Treatment included lipid lowering therapy and management of RA. It is important to recognize the association between rheumatologic manifestations and familial hypercholesterolemia for diagnostic and therapeutic reasons.

Keywords: Arthritis, familial hypercholesterolemia, statin, atherosclerosis

Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder characterized by extremely elevated levels of low-density lipoprotein cholesterol (LDL-C) and a propensity to early onset atherosclerotic cardiovascular disease. According to the American Heart Association, the clinical diagnosis of FH includes LDL-C > 190 mg/dl and a first-degree relative with either LDL-C > 190 or known premature coronary heart disease [1]. Homozygous FH is a very rare disease with a poor prognosis, but heterozygous FH is a relatively common disorder, affecting about 0.2% in most countries [2]. FH may be misdiagnosed as RA because of swelling in the joints and periarticular area or mimic arthritis or rheumatoid nodules, but despite treatment for RA, the swellings can increase in size [3, 4]. Herein, we report a patient with FH presenting with seropositive rheumatoid arthritis. To the best of our knowledge, this association has rarely been reported. The clinical manifestations, investigative findings, and treatments are reviewed in this paper.

Case Presentation

In 2015, a 36-year-old woman referred to a rheumatologist with three weeks of severe right knee and toe pain. She denied any skin rash, oral ulcer, color changes in her extremities, dyspnea, or trauma. The patient had a history of joint pain and swelling, which healed in a few days with nonsteroidal anti-inflammatory drugs (NSAIDs). She was a known case of FH and at age 27 had coronary artery bypass grafts. She was treated with metoprolol, aspirin, losartan, nitroglycerin, gemfibrozil, and atorvastatin. There was no consanguinity between her parents. The patient had six siblings and a family history of hypercholesterolemia and premature coronary heart disease in her mother and two sisters but no family history of RA. Thirteen years prior, the patient’s sister died at the age of 27 from heart disease and hyperlipidemia.

In physical examinations, the patient was afebrile but had severe knee and toe tenderness. Numerous xanthomas lesions in the hands (Figure 1) and elbows, and xanthelasma in eyelids and corneal arcus in eyes (Figure 2) were observed. Lab data is shown in Table 1.

Based on the patient’s history, physical examination, and laboratory tests, palindromic rheumatism was diagnosed and treatment was initiated with prednisolone and hydroxychloroquine. The patient reported improvement in articular symptoms. The statin dose reached its maximum. One year later, both knees and the right little finger were affected by pain and swelling. In this time, the patient’s lipid profile included cholesterol: 850 mg/dl, low density lipoprotein: 504 mg/dl, increased acute phase reactant (ESR: 48, CRP: pos), negative ANA, anti-dsDNA, and RF, and remarkably high anti-CCP: 67 u/ml (ULN = 5). The patient was diagnosed with rheumatoid arthritis based on the 2010 ACR/EULAR classification criteria for rheumatoid arthritis [5]. Articular involvement was controlled by low doses of prednisolone, hydroxychloroquine, and methotrexate. Four years later, some changes...
in xanthoma and xanthelasma size and shape occurred during treatment with lipid lowering agents (Figure 3); however, despite taking lipid lowering drugs, cholesterol levels were not controlled.

Informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Figure 1. Numerous xanthomas lesions in the hand

Figure 2. Xanthelasma and corneal arcus

Figure 3. Changes in xanthomas and xanthelasma during treatment with lipid lowering agents in first visit and 4 years later

Table 1. Laboratory tests of the patient

<table>
<thead>
<tr>
<th>CBC</th>
<th>WBC: 6800, Hg: 11 g/dl, Plt: 238000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute phase reactants</td>
<td>ESR: 12 mm/h, CRP: neg</td>
</tr>
<tr>
<td>Cholesterol: 668 mg/dl, low density lipoprotein: 524 mg/dl, high density lipoprotein: 80 mg/dl, triglyceride: 135 mg/dl, creatinine: 0.8 mg/dl. ALT: 30 IU/L, calcium: 9.6 mg/dl.</td>
<td></td>
</tr>
<tr>
<td>Rheumatologic tests</td>
<td>TSH: 2.1 Mu/l (0.46)</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>HBs Ag: neg, HCV Ab: neg,</td>
</tr>
<tr>
<td>Viral markers</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>No abnormalities.</td>
</tr>
</tbody>
</table>
Discussion

The diagnosis of familial hypercholesterolemia was based on clinical presentation, family history, and laboratory data. In the current patient, the diagnosis of RA was made on the basis of clinical and laboratory findings. Our patient first developed palindromic rheumatism and then rheumatoid arthritis (arthritis, elevated acute phase reactant, anti-CCP positivity, and duration of manifestations) [5]. To the best of our knowledge, this case is the third report of a patient with this association.

The first reported case was a 51-year-old man with a history of type IIa hyperlipidemia and chronic symmetrical destructive polyarthritis of the peripheral joints, high ESR, positive RF and Schirmer’s test, and several foci mononuclear cells of glandular tissue in the minor salivary gland biopsy. The patient was diagnosed with rheumatoid arthritis and Sjogren’s syndrome [6].

The second case was a 59-year-old woman with FH who developed RA and presented with marked tendinitis of the Achilles tendons, patellar tendons, and finger extensor tendons at the onset of RA [7].

In a study on 48 patients with FH, tendon xanthomas and Achilles tendinitis were more common in patients than in controls, but migratory polyarthritis was rare [8]. FH is characterized by a decreased removal of low-density lipoproteins. One of the hallmarks of the disease is tendinous xanthomata. In a study on 73 patients with heterozygote FH, about 40% had at least one episode of articular symptoms, including Achilles pain, Achilles tendinitis, oligoarticular arthritis, polyarticular, or rheumatic fever-like arthritis [9]. In one study on 166 patients with hyperlipidemia attending a lipid clinic, eight males with type IV hyperlipidemia had recurrent acute attacks of gout, and a transient recurrent polyarthritis was reported in 3 patients with type IV and type II hyperlipidemia which consisted of brief episodes of swelling in the small joints of the hands that lasted no more than 2-3 days each time [10].

Both innate and adaptive immune responses have been found to play a key role in the initiation and progression of atherogenesis. In FH patients, the accumulation of cholesterol crystals and oxLDL in the vessels is particularly high, with consequent abnormal mobilization of immune cells and secretion of various pro-inflammatory and chemokines [11]. Evidence suggests that macrophages from FH patients with tendon xanthomas exhibit a differential gene expression profile characterized by increased plasma tryptase, TNF-α, IL-8, and IL-6 expression [12].

FH itself and lipid-lowering agents may be associated with articular and periarticular manifestations, but in the present case, the joint symptoms revealed no association because of long term hypercholesterolemia and the patient’s use of statins. Tendon side effects due to statins occur within the first year of drug use [13]. Some evidence points to the potential benefits of statins on RA disease activity due to their immunomodulatory and anti-inflammatory properties [14, 15].

According to some similarities between the manifestations of FH and RA in articular and/or soft tissue lesions, patients with FH and arthropathies should also be monitored for systemic connective tissue disorders.

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Conflict of Interest

The authors declare no conflicts of interest.
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References


