Successful Treatment with Tocilizumab in a Case of Intralymphatic Histiocytosis Associated with Rheumatoid Arthritis

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Abstract

A 75-year-old woman with rheumatoid arthritis (RA) presented with long-term painful erythema on the right upper arm and left elbow. The patient was diagnosed with intralymphatic histiocytosis (ILH) based on the biopsy findings. Because the patient was unresponsive to single-agent treatment with methotrexate, infliximab and etanercept, we switched to tocilizumab (TCZ) treatment, which induced remission of the ILH. Our case suggests that TCZ may be a treatment option for ILH in patients with RA.

Key words: intralymphatic histiocytosis, rheumatoid arthritis, tocilizumab

(Intern Med 53: 2255-2258, 2014)
(DOI: 10.2169/internalmedicine.53.2688)

Introduction

Intralymphatic histiocytosis (ILH) is a benign, chronic skin disease characterized by the presence of mononuclear histiocytes in dilated dermal lymphatic vessels. ILH has been reported to be a rare cutaneous manifestation of rheumatoid arthritis (RA), but its etiology and treatment have yet to be established. While some cases of spontaneous remission of ILH have been reported, refractory and even incurable cases are also known. Recently, Sakaguchi et al. (1) reported the clinical efficacy of infliximab (IFX) for a refractory case of ILH associated with RA, thus suggesting that inflammatory cytokines may play a role in the development of ILH. In the present report, we describe a case of refractory ILH in association with RA that was successfully treated with the humanized anti-IL-6 receptor tocilizumab (TCZ).

Case Report

A 75-year-old woman visited a nearby clinic in 2003 due to swelling and pain in the bilateral ankle joints. She was diagnosed with remitting seronegative symmetrical synovitis with pitting edema syndrome, possibly due to the fact that she was of older age and was rheumatoid factor-negative. Treatment with corticosteroids (prednisolone 10 mg/day) was started and her symptoms promptly disappeared. Her steroid dose was tapered over one year, but after discontinuation she developed polyarthritis again in her left elbow, right shoulder, and bilateral knee joints. Simultaneously, erythema appeared on her right upper arm and left elbow. She was treated with intra-articular corticosteroid injection and oral prednisolone, but her symptoms did not improve. In August 2008, she visited our hospital. Although both the rheumatoid factor and anti-cyclic citrullinated protein (CCP) antibody were negative, joint X-rays revealed multiple bone erosions (left wrist, left carpometacarpal and right shoulder joint) and joint space narrowing (left wrist and left elbow). In addition, right shoulder magnetic resonance imaging revealed synovial membrane proliferation. We therefore diagnosed her with seronegative RA. She was started on weekly doses of methotrexate (MTX), which was later increased to 10 mg per week, but her arthritis and erythema, which had not been previously treated with topical therapy, did not respond. We considered erythema rheumatoid vasculitis or cu-
Figure 1. Time course changes in the patient’s right upper erythema: (a) just after the biopsy; (b) before treatment with tocilizumab; and (c) after treatment with tocilizumab.

Figure 2. The histopathological findings of the patient’s skin biopsy specimens (200×). (a) Vessels in the dermis are dilated and inflammatory cells, such as lymphocytes, plasma cells and macrophages, are present. Histiocytic cells accumulated in one of the vessels (*). These histiocytic cells showed no indications of malignancy. (b) Intravascular histiocytic cells stained with CD68 (*). (c) Endothelial cells of dilated vessels stained with D2-40.

taneous lymphoma as a possible complication and a skin biopsy from an area of the erythema (Fig. 1a) was done in January 2009. In the sample, we found an accumulation of histiocytic cells in the enlarged vessels (Fig. 2a); these cells showed no evidence of malignancy. Furthermore, these cells in the vessels were positive for CD68 (Fig. 2b), an immunological marker for histiocytes, and endothelial cells of the vessels were positive for D2-40 (Fig. 2c), a maker for lymph ducts. Based on these findings, we diagnosed her erythema as ILH. In February 2009, she was started on low
dose IFX (3 mg/kg). She responded well and her 28-joint disease activity score-erythrocyte sedimentation rate (ESR) (DAS28-ESR) fell from 5.5 to 3.12. The erythema on her left elbow disappeared, but the one on her right upper arm remained. In September 2009, her joint pain worsened and the erythema on her right upper arm was exacerbated despite treatment with an increased dose of IFX (5.5 mg/kg).

In March 2010, the patient’s treatment was switched from IFX to Etanercept (50 mg/week) under continuous treatment with MTX, but had no effect on the arthritis or right upper erythema. She was admitted to our hospital in June 2010 to determine a new treatment strategy. On admission, she had severe erythema on her right upper arm with tenderness (Fig. 1b) and her left elbow joint was swollen. The patient’s inflammatory markers were ESR: 87 mm/h; C-reactive protein: 5.7 mg/dL; and matrix metalloproteinase-3: >800 ng/mL. The patient’s RA was moderate with a DAS 28-ESR of 4.26. Because anti-tumor necrosis factor (TNF) blockers were not effective, her treatment was changed to the IL-6 blocker TCZ (8 mg/kg). During combination therapy of TCZ and MTX, the patient’s DAS28-ESR dramatically decreased to <2.6. In October 2010, in addition to improvement of her arthritis, her erythema improved gradually and disappeared in December 2010 (Fig. 1c). At the latest follow-up, almost 3 years after the first initiation of TCZ, the patient remained in remission with no relapse of the ILH.

**Discussion**

ILH is a rare cutaneous disorder accompanying RA which is characterized by erythema with an unclear border around joints and sometimes papules or induration. The characteristic pathological feature of ILH is the accumulation of histiocytes in the lymph ducts in the dermis. ILH was first reported in 1994 by O’Grady et al. (2). At that time, they used the term “intravascular histiocytosis” (IVH) since they did not distinguish the lymph ducts from the blood vessels. In 2005, Okazaki et al. (3) stained vascular endothelial cells in IVH with D2-40, a marker for lymphatic endothelial cells, and showed that the vasculature in which the histiocytes accumulated were the lymph ducts.

ILH was thought to be an intravascular lymphoma when O’Grady et al. (2) first reported this rare condition. ILH is no longer regarded as a malignant disease but as a reactive change to inflammation; it is sometimes thought to be an aspect of intravascular reactive angioendotheliomatosis (RAE) (4). RAE is a rare cutaneous disorder whose histopathological features resemble those of ILH. However, RAE should be regarded as a disease entity distinct from ILH because proliferating cells in the vessels during RAE are not histiocytes but endothelial cells, and these endothelial cells are thought to proliferate as a reaction to infection, such as tuberculosis or subacute bacterial endocarditis (5). The most frequent underlying disease of ILH is RA, but other causes, such as a breast cancer (4) and replacement arthroplasty (6), have been reported. The cause of ILH has yet to be eluci-

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**Table. Summary of the Cases from the Literature of RA Patients with ILH**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>RA disease activity</th>
<th>Lesion of ILH</th>
<th>Clinical course of ILH</th>
<th>Usage of MTX</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66/F</td>
<td>+</td>
<td>Right elbow</td>
<td>Disappeared by IFX</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>51/M</td>
<td>+</td>
<td>Left knee</td>
<td>ND</td>
<td>−</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>79/F</td>
<td>ND</td>
<td>Thighs and knees</td>
<td>Disappeared by knee replacement</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>46/F</td>
<td>ND</td>
<td>Left lower leg</td>
<td>ND</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>57/F</td>
<td>ND</td>
<td>Left thigh</td>
<td>ND</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>84/F</td>
<td>ND</td>
<td>Right upper arm</td>
<td>ND</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>73/M</td>
<td>ND</td>
<td>Left upper arm</td>
<td>ND</td>
<td>ND</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>60/F</td>
<td>+</td>
<td>Left thigh and lower leg</td>
<td>Spontaneously disappeared</td>
<td>+</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>50/F</td>
<td>+</td>
<td>Thighs</td>
<td>Disappeared by oral pentoxifylline</td>
<td>−</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>75/F</td>
<td>ND</td>
<td>Left forearm</td>
<td>ND</td>
<td>−</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>46/F</td>
<td>−</td>
<td>Right forearm</td>
<td>ND</td>
<td>+</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>70/M</td>
<td>+</td>
<td>Left elbow</td>
<td>Diminished by topical CS</td>
<td>−</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>63/F</td>
<td>ND</td>
<td>Left elbow and left forearm</td>
<td>Diminished by topical CS</td>
<td>+</td>
<td>14</td>
</tr>
<tr>
<td>14</td>
<td>71/F</td>
<td>+</td>
<td>Right forearm</td>
<td>Disappeared by a pressure bandage and topical diflorasone diacetate</td>
<td>+</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>74/F</td>
<td>+</td>
<td>Left elbow and right upper arm</td>
<td>Partially diminished by IFX and disappeared by TCZ</td>
<td>+</td>
<td>*</td>
</tr>
</tbody>
</table>

ND: not described, IFX: infliximab, CS: corticosteroid, TCZ: tocilizumab, MTX: methotrexate, Ref: reference number, *: our case
dated, although it is speculated that lymphatic drainage of inflammatory cells may be involved in its development in RA (7). The treatment of ILH has not been established; however, in some cases ILH spontaneously disappears (7-9). As shown in Table, there have been 15 cases of definite ILH associated with RA reported since the study by Okazaki et al. (1, 3, 6, 8, 10-15). Closer examination of these cases revealed that patients whose RA activity was high and older women tended to suffer from ILH. These tendencies were consistent with the present case. Although our patient was seronegative RA, there was no association between ILH and being positive for rheumatoid factor or anti-CCP antibody. ILH lesions do not necessarily correlate with active arthritis. Because ILH has developed both in MTX-treated and MTX-untreated RA patients, we surmise that the use of MTX is not closely associated with the development of ILH. Our patient’s joints improved and her erythema disappeared following a switch from anti-TNF blockers to TCZ, which suggests that IL-6 may play an important role in the pathogenesis of ILH. To the best of our knowledge, this is the first report of the efficacy of TCZ for refractory ILH associated with RA. Further clinical cases are needed to verify the efficacy of TCZ for ILH in patients with RA.

The authors state that they have no Conflict of Interest (COI).

References