

Ustekinumab-induced chronic lymphocytic leukemia in a patient with psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by skin and joint involvement. The disease may present with various joint pattern involvement, which sometimes may lead to joint destruction and deformity. Early diagnosis and treatment with disease-modifying antirheumatic drugs may prevent joint deformity. Recently there are many new treatment options including biologic drugs. Ustekinumab, an interleukin 12/23 inhibitor, has proven efficacy in the treatment of psoriatic arthritis. Like other biologic drugs (anti-TNF- α), there are contradictory data about the safety of ustekinumab and possible relationship with cancer development. Herein we report the development of chronic lymphocytic leukemia in a patient with PsA treated with ustekinumab.

Key words: psoriatic arthritis, ustekinumab, chronic lymphocytic leukemia.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease, mainly affecting the skin and musculoskeletal system [1]. Its incidence in the general population is reported to vary between 2 and 3% [2]. Environmental and genetic factors are considered to play a role in the etiology, although it is not fully known yet.

The mechanisms that are considered to be responsible for the immunopathogenesis of the disease include the activation of T cells, particularly in the skin and joints, causing the secretion of many pro-inflammatory cytokines such as tumor necrosis factor α (TNF- α), interleukin 17 (IL-17) and interleukin 12/23 (IL-12/23). Systemic treatment with disease-modifying antirheumatic drugs (DMARDs) is required to control the clinical findings and increase the quality of life [3].

The long-term use of conventional DMARDs such as methotrexate and cyclosporine is limited due to dose-related toxicity and secondary inefficacy. Recently, a clearer understanding of the pathogenesis of PsA and inflammatory cytokine pathways supported the de-

velopment of biological therapies [4]. These therapeutic agents affect various steps in the immunopathogenesis of PsA, namely by inhibiting TNF- α , IL-17 and/or the IL-12/23 pathway.

Ustekinumab is a human IgG1 κ monoclonal antibody that blocks the biological activity of interleukin 12 and interleukin 23 by acting on T cells, natural killer cells and receptors on antigen presenting cells [5].

Interleukin 12 and interleukin 23 are involved in the differentiation of Th1 and Th17 cells. Interleukin 12 is an inflammatory cytokine involved in both natural and adaptive immune responses and it consists of two subunits called p35 and p40 [6]. The efficacy and safety of ustekinumab in the treatment of psoriasis and psoriatic arthritis have been shown [7].

However, some immune and paradoxical reactions due to use of ustekinumab have been reported [8]. One of the major concerns of ustekinumab use is their potential of increasing the risk of cancer development. The relationship between ustekinumab and malignancy is not clear yet.

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Material and methods

We analyzed studies reporting development of chronic lymphocytic leukemia due to ustekinumab use in psoriatic arthritis from PubMed and Google Scholar databases as key words using a combination of search terms such as: psoriatic arthritis, leukemia, and ustekinumab.

Using a combination of presented search terms, we undertook a systematic review of the literature for discussion and analysis of studies reporting ustekinumab related chronic lymphocytic leukemia and/or hematologic malignancy in psoriatic arthritis patients.

Case description

A 66-year-old male patient was referred to our Hematology Outpatient Clinic with complaints of fatigue, skin lesions and weight loss. According to the patient's medical history he was followed up with PsA diagnosed until the year 2010 (Fig. 1).

The patient was treated with methotrexate (MTX) during the years 2010–2012 and thereafter with etanercept for his active psoriatic arthritis. In 2013 the etanercept was stopped because of secondary inefficacy and ustekinumab was started.

Two years later during ustekinumab treatment, the patient was admitted to the Hematology Outpatient Clinic because of complaints of fatigue, skin lesions, weight loss and abnormal findings of the blood tests.

On physical examination, skin lesions compatible with psoriasis were seen. The spleen and liver were not palpable. Auscultation revealed normal lung sounds, and a regular cardiac rhythm, with no murmurs.

Laboratory test results were as follows: erythrocyte sedimentation rate (ESR): 45 mm/h, C-reactive protein (CRP): 12 mg/dl (normal range 0–5 mg/dl), leukocyte: 13 700/ μ l, lymphocyte: 6700/ μ l, Hb: 13.5 g/dl, Htc: 39.5%, Plt: 285,000/ μ l. Urinalysis, liver and kidney function tests were normal, and lactate dehydrogenase (LDH) was 183 U/l (normal range 1–140 U/l).

Peripheral blood smear and bone marrow biopsy showed leukocytosis, with lymphocytes at a rate of 67%, where the majority were small and mature and some were of medium size.

Erythrocytes were normochromic normocytic and platelets were adequate in number, with normal distribution. Flow cytometric analysis was positive for CD5, CD19, CD20 and CD5+, CD19, which was consistent with stage 0 chronic lymphocytic leukemia (CLL).

Ustekinumab-related CLL was suspected and ustekinumab treatment was discontinued and low-dose corticosteroid and MTX was started for his PsA. The patient's symptoms regressed; the fatigue and skin lesions disappeared almost totally.

Follow-up laboratory test results were as follows: ESR: 25 mm/h, CRP: 3 mg/dl (normal range 0–5 mg/dl), leukocyte: 8300/ μ l, lymphocyte: 4700/ μ l, Hb: 14.5 g/dl, Htc: 39.4%, Plt: 292,000/ μ l, and LDH was 122 U/l (normal range 1–140 U/l). Peripheral blood smear showed normal cell distribution. The patient's follow-up is ongoing at the hematology and rheumatology outpatient clinics.

Results

We analyzed similar clinical problems in the literature. There have been only five case reports published in the literature regarding ustekinumab-related hematologic malignancy development. None of these cases reported the development of CLL due to ustekinumab use. Our study is the first report on this problem.

Discussion

Psoriatic arthritis is a chronic inflammatory disease characterized by skin and joint involvement. The results of observational studies and a large-scale meta-analysis revealed that patients with psoriasis and PsA carry the risk of developing malignancies, including lymphoma and skin cancer such as melanoma [9]. Whether the risk of malignancy is related to the disease itself or to immunosuppressive systemic therapy is still controversial [10].

In recent years, biologic drugs have revolutionized the treatment of PsA and made significant clinical,



Fig. 1. Psoriatic arthritis involvement and deformity of the hand joints.

Table I. Important reports in the literature regarding ustekinumab and hematologic malignancy

Patient diagnosis	Patient age/gender	Disease duration (years)	Treatment drugs before ustekinumab	Malignancy type	Malignancy diagnosis	Outcome	References
Pityriasis rubra pilaris	50/female	14 years	Corticosteroids	Anaplastic large T-cell lymphoma	Skin biopsy	Good	Humme et al. [13]
Crohn's disease	29/female	8 years	Azathioprine Corticosteroids Infliximab	Malignant melanoma	Skin biopsy	Good	Ehmann et al. [14]
Crohn's disease	29/female	12 years	Azathioprine Methotrexate Corticosteroids Vedolizumab	Anaplastic large T-cell lymphoma	Inguinal lymph node	Good	Smeets et al. [16]
Psoriasis	68/male	13 years	Efalizumab Methotrexate	MALT lymphoma	Gastric biopsy	Died of cerebral infarction	González-Ramos et al. [17]
Psoriatic arthritis	66/male	20 years	Methotrexate Etanercept	CLL	Bone marrow biopsy + FCA	Good	Current case

CLL – chronic lymphocytic leukemia, FCA – flow cytometric analysis, MALT – mucosa-associated lymphoid tissue.

laboratory and radiological remission possible. Interleukin 12 and interleukin 23 are among the cytokines playing a central role in regulation of the T cell immune response and have an important role in the pathogenesis of psoriatic arthritis.

Ustekinumab is an interleukin 12/23 antagonist which has proven efficacy in the treatment of psoriatic arthritis [11].

There are few and contradictory data about the relationship between ustekinumab and hematologic malignancy development (Table I).

Florek et al. [12] reported various adverse events of 10 years of ustekinumab use in the postmarketing period. Among these events of importance are some malignancies such as B-cell lymphoma, epithelioid sarcoma, lung and thyroid cancer. This report's strength is that it represents real-world data, contrary to randomized controlled trials.

Thus, it should be emphasized that these strong findings indicate a possible relationship between ustekinumab and malignancy, but not causality. Also there are some reports of ustekinumab-related hematologic malignancy in various diseases.

Humme et al. [13] reported CD30-positive anaplastic large cell T-cell lymphoma under ustekinumab therapy for pityriasis rubra pilaris. The ustekinumab was stopped and the patient received CHOEP (cyclophosphamide, hydroxydaunorubicin, oncovin, etoposide, prednisone) chemotherapy.

Ehmann et al. [14] reported malignant melanoma during ustekinumab therapy of Crohn's disease. Scherl et al. [15] reported some cases of malignancies of the

prostate, thyroid and colon, while hematologic malignancy was not seen. Smeets et al. [16] reported anaplastic large T-cell lymphoma in a patient with Crohn's disease during ustekinumab treatment. Treatment with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) was initiated. Unfortunately, the patient had a refractory lymphoma and proceeded to allogeneic stem cell transplantation.

González-Ramos et al. [17] presented gastric mucosa-associated lymphoid tissue lymphoma in a patient with severe psoriasis receiving ustekinumab. The described patient received 19 sessions of radiation therapy, which resulted in complete remission of the disease. Chronic lymphocytic leukemia, as diagnosed in the presented case, has not been observed so far.

Other studies found no significant relationship between ustekinumab and the risk of malignancy [18]. The contradictory results reported in the studies are explained with various reasons: patient selection, type and duration of disease, family history of malignancy and use of another immunosuppressive drugs.

It should be noted that a limitation of the analysis is still the relatively short time of using ustekinumab in the treatment of psoriatic arthritis.

Conclusions

This presentation reports occurrence of CLL in a patient with PsA treated with ustekinumab which may point to plausible time relation with use of this drug. However, this is only "possible" but not "certain" causality.

So, far there have been no unequivocal associations of ustekinumab with the development of malignancy in the available literature. At present, many studies and observations are inconsistent and the study groups are incomparable with each other.

In this subject further observations in real life studies and in the longer period of time are needed.

The authors declare no conflict of interest.

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