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Single Case

Flare-Up of Rheumatoid Arthritis by Anti-CTLA-4 Antibody but Not by Anti-PD1 Therapy in a Patient with Metastatic Melanoma

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Keywords

Melanoma · Rheumatoid arthritis · Immunotherapy · Ipilimumab · Pembrolizumab

Abstract

A 47-year-old female patient with rheumatoid arthritis (RA) treated with methotrexate, was diagnosed with metastatic melanoma. After surgical removal of the tumor, the patient started treatment with ipilimumab while methotrexate was stopped. One week after initiation of ipilimumab, the patient developed typical symptoms of RA. Analgetic therapy was started. After 4 cycles of ipilimumab, melanoma progression was radiologically evident. The treatment plan was changed to pembrolizumab (anti-PD1 antibody), and the patient did not show active signs of RA anymore. Despite treatment with pembrolizumab, the patient died 4 months later due to tumor progression. The exact mechanism by which ipilimumab (anti-CTLA-4 antibody) provoked RA symptoms is still not fully understood. This subject needs more investigation, especially in an era in which immunotherapies are a standard therapy for patients with malignancy.

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Introduction

Rheumatoid arthritis (RA) is a chronic, T-cell mediated autoimmune disease characterized by extensive synovitis, resulting in the destruction of joint cartilage and bone [1]. Although the pathogenesis of RA remains poorly understood, the importance of the costimulatory molecules CD28 and CTLA-4 in the disease process has been demonstrated [2]. The worsening of RA in a patient treated with ipilimumab for metastatic melanoma has been previously described in the literature [3].

Ipilimumab and pembrolizumab are both immunotherapeutic agents used for the treatment of metastatic melanoma. These agents act on 2 different immune checkpoint regulators. Ipilimumab is a monoclonal antibody that blocks the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) on T cells and therefore enhances an antitumor immunity by activating T-lymphocyte proliferation. Pembrolizumab is a fully humanized monoclonal antibody that inhibits the programmed death-1 receptor (PD-1) on T-cells resulting in an increased tumor-specific immune response [4].

In this report, we describe a case of a patient who experienced increased RA activity during ipilimumab treatment, but stable RA activity during pembrolizumab for metastatic melanoma.

Case Report

A 47-year-old woman with RA who was being treated with methotrexate, was diagnosed with a spitzoid melanoma in March 2004 and the tumor was surgically removed. In 2010, the RA treatment was changed to infliximab (Remicade). After almost 10 years of a tumor-free period, the patient returned to our clinic in May 2013 with swollen left axillary lymph nodes. Nodal metastasis was confirmed after fine-needle aspiration. A PET scan showed pulmonary, liver, and subcutaneous metastasis as well. Infliximab was stopped and metastasectomy of the left axilla was performed. Treatment with ipilimumab was started at 3 mg/kg every 3 weeks for 4 cycles in an expanded access program in August 2013. One week following the first injection of ipilimumab, the patient developed classic symptoms of severe arthritis affecting both hands and feet as well as both knees. Clinically, the patient showed swelling and redness of all extremities. The right knee was painful but with good range of motion. Inflammatory markers were elevated with a C-reactive protein (CRP) of 35 mg/L (N <5 mg/L) and no sign of leukocytosis. No radiological joint scan was performed at this point. An anti-inflammatory and analgesic therapy with a nonsteroidal anti-inflammatory drug (ibuprofen) was prescribed and a local injection of corticosteroids in the knee was performed. Furthermore, the patient was started on sulfasalacin (2 g/day) for RA. After 4 cycles of ipilimumab, melanoma progression was radiologically confirmed in February 2014, and dacarbacin 1,600 mg was given every 3 weeks from April 2014 for a period of 3 months. In August 2014, the patient underwent treatment with pembrolizumab (2 mg/kg) every 3 weeks following recurrent disease progression. The symptoms of RA remained always under control with no signs of active disease. Nevertheless, the patient died 4 months later due to tumor progression.

Discussion

We described a melanoma patient with exacerbation of her RA upon treatment with ipilimumab, on the other hand, RA activity was stabilized when she was treated with pembrolizumab. RA is considered a CTLA-4+ T helper cell disease. These cells are found in large numbers in the synovial milieu in all patients with RA [5]. The exact mechanism by which the anti-CTLA drug ipilimumab provokes underlying RA symptoms is still not completely understood. CTLA-4 is thought to regulate T-cell proliferation early, whereas PD-1 suppresses T cells later in the immune response [6]. The importance of the CTLA-4/CD28 axis for the pathologic mechanism of RA has been demonstrated by the successful application of abatacept, which is a fusion protein composed of the Fc region of the immunoglobulin IgG1 linked to the extracellular domain of CTLA-4 [7]. In fact, abatacept prevents the binding of CD28:B7 (CD80/86), which blocks the activation of T helper cells [2, 8]. The hypothesis we suggest for ipilimumab-induced aggravation of pre-existing RA is that anti-CTLA-4 blocks competitively the binding of CTLA-4:B7 (CD80/86) on T helper cells. This can prevent the inhibitory signal normally provided by CTLA-4:B7 binding and leads to T-cell activation by the CD28-B7 crosstalk and subsequently to increased levels of IFNγ, IL2, and IL-17 in the peripheral blood and in the synovial milieu of patients with RA [1, 2]. Although in this case ipilimumab appeared to exacerbate RA, a series of previous reports suggest that melanoma patients could benefit from ipilimumab without signs of aggravation of any underlying autoimmune disorders [3, 9, 10].

This topic is of special importance, since patients with active autoimmune disorders are frequently excluded from clinical trials with immunotherapies. Therefore, there is a lack of data on how their autoimmune disorders might be affected by immunotherapy.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the study apart from those disclosed.

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