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CASE REPORT

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Hypersensitivity reaction against influenza vaccine in a patient with rheumatoid arthritis after the initiation of etanercept injections

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Abstract A 58-year-old Japanese woman with rheumatoid arthritis (RA) suffered from high fever triggered by administration of an influenza vaccine after a 4-month-long effective treatment course with the TNF-α inhibitor etanercept. Influenza vaccine had been previously administrated safely to the patient before initiation of etanercept therapy. The fever occurred without other symptoms soon after vaccine administration, progressed to high fever 1 day later, and spontaneously resolved the second day. The clinical course appears to be compatible with drug fever closely associated with immediate hypersensitivity (in particular, late-phase type I allergic reaction), in which T helper (Th) 2 cells play a crucial role. Etanercept can strongly suppress Th1-mediated reactions; therefore, Th2 activity may be augmented by etanercept treatment in aspect of antagonism between Th1 and Th2 mechanisms. In RA patients who receive treatment with TNF-α inhibitor such as etanercept, activation of Th2-mediated immune responses such as immediate hypersensitivity may be a necessary side effect for those who receive vaccinations.

Key words Etanercept · Hypersensitivity · Influenza vaccine · Rheumatoid arthritis (RA) · T helper (Th) 1 · T helper (Th) 2

Introduction

Rheumatoid arthritis (RA) is an autoimmune polyarthritis characterized by T helper (Th) 1 dominance that offsets the Th1/Th2 balance.[1] In particular, tumor necrosis factor (TNF)-α, which tips the balance toward Th1-mediated responses, plays a crucial role in the pathogenesis of RA. Recently, RA therapies that inhibit TNF-α activity, including etanercept (recombinant TNF-α receptor fused with the Fc domain of human immunoglobulin G [IgG] 1), have been introduced, with demonstrated therapeutic effectiveness in refractory RA patients.[2]

In this report, we describe an RA patient who suffered from high fever, which may have been triggered by hypersensitivity against an influenza vaccine, during a successful etanercept treatment course. We also discuss potential mechanisms of hypersensitivity during etanercept treatment.

Case report

A 58-year-old Japanese woman was admitted to our hospital in November 2005 with a 2-day history of high fever spikes. She had been diagnosed with RA in 1997. Several disease-modifying antirheumatic drugs, including bucillamine, mizoribine, and salazosulfapyridine, had not been effective, and bilateral total knee arthroplasty (TKA) was performed in 2003. Soon after TKA, treatment with 11.25 mg/week of methotrexate (MTX) was initiated, and polyarthritis began to improve. However, MTX pneumonia developed 3 months later, so MTX treatment was stopped. Methotrexate pneumonia resolved, although mild sequelae in the lung remained. Following discontinuation of MTX therapy, polyarthritis recurred progressively and treatment with etanercept (25 mg/day, twice weekly, subcutaneous injection) was initiated in July 2005. Therapeutic efficacy of etanercept with concomitant administration of prednisolone (7 mg/day) was apparent immediately, and polyarthritis resolved. Serum C-reactive protein (CRP) levels decreased to approximately 1 mg/dl until the current admission. No adverse events, including injection site reactions, were detected. Two days before the current admission, both etanercept (25 mg) and inactivated influenza vaccine (15 μg) were injected subcutaneously on opposite upper arms. That

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evening, the patient felt febrile. The next day, fever progressed without other manifestations, and body temperature reached 39°C. On the morning of admission (i.e., 2 days after vaccine administration), the fever began to resolve spontaneously. The patient visited our hospital that day and was admitted. During the previous year, before etanercept treatment was initiated, the patient had received an influenza vaccine without adverse events. Her allergic history included hypersensitivity to sulpyrine.

On admission, the patient was alert, orientated, mildly febrile (37.0°C), and normotensive (135/91 mmHg) with a regular heart rate of 106 beats/min. Examination of the oral cavity and pharynges was unremarkable. Lymph node swelling in the neck was absent. Examination of the chest and abdomen was unremarkable, and there was no edema of the lower extremities. There were no apparent skin lesions, including those that may have been indicative of an injection site reaction. No cost-vertebral angle tenderness was detected. Morning stiffness disappeared within a few minutes, and joint tenderness and swelling were not observed.

Laboratory findings were as follows: white blood cell count, 19400/μl (eosinophil, 252/μl); hemoglobin, 16.3 g/dl; platelet count, 21.2×10^4/μl; total protein, 7.5 g/dl; total bilirubin, 1.0 mg/dl; aspartate aminotransferase, 18 U/l; alanine aminotransferase, 24 U/l; lactic dehydrogenase, 440 U/l; creatine phosphokinase, 69 U/l; amylase, 96 U/l; blood urea nitrogen, 20 mg/dl; creatinine, 1.4 mg/dl. Serum electrolytes and fasting blood sugar were normal. Serological findings were as follows: CRP, 34.70 mg/dl (normal range <0.5 mg/dl); IgG, 974 mg/dl; IgA, 217 mg/dl; IgM, 84 mg/dl; rheumatoid arthritis hemagglutination assay, 1:160; and anti-streptolysin O, <40 U. Cytomegalovirus antigen and β-D-glucan were negative. Urine sediment revealed no evidence of urinary tract infection. Influenza virus antigen was negative. Chest X-ray showed mild infiltration on the right lower lung field, as detected previously.

During the night of the first day of admission, the fever spontaneously resolved. Fever did not recur, and serum CRP level decreased to 1.98 mg/dl on day 6. Etanercept treatment was halted after admission, and mild polyarthralgia began to recur by day 7. On day 7, treatment with etanercept (25 mg/day, twice weekly) was reinitiated, and the patient was discharged. Her articular symptoms were improved by the following week. A diagnosis of hypersensitivity (so-called drug fever) against the influenza vaccine was proposed as being responsible for the high fever, because it occurred soon after the vaccine was administrated, and it remitted in a self-limited manner within 2 days: further, no other etiologies, including infectious diseases, were detected.[3,4] A drug-induced lymphocyte stimulation test (D-LST) against the influenza vaccine was performed on day 10 (11 days after vaccine administration), and a positive result was obtained (955%, 8001 cpm; control, 837 cpm). Two months after discharge, treatment with etanercept was continued effectively with no further sequelae.

Discussion

Drug fever is the most common result of hypersensitivity against an administered drug, and it possesses certain characteristics that are similar to allergic reactions.[3,4] Drug fever is usually accompanied by other manifestations, such as rash, urticaria, and eosinophilia, although fever not associated with any other symptoms may also occur.[4] Allergic reactions are commonly classified into four different categories according to their associated immune response patterns: immediate hypersensitivity reactions (type I), antibody-mediated reactions (type II), immune complex-mediated reactions (type III), and T-cell-mediated reactions (type IV).[5] Clinically, hypersensitivity is usually complex, most often due to the combination of several different types of immune reactions.[5] Among the four types of allergic immune responses, immediate hypersensitivity responses (type I) occur the soonest after antigen exposure, and consist of both immediate and late phase.[6] The immediate phase occurs minutes after antigen exposure, while the late phase begins 2–4 h after antigen exposure, is maximal about 24 h after exposure, and then gradually subsides.[6] Late-phase immediate hypersensitivity reactions (type I) may occur without a detectable preceding immediate phase.[6] The second fastest allergic immune responses are antibody-mediated responses (type II), which occur a few days after antigen exposure.[6] In our case, fever manifested as hypersensitivity occurred soon after injection of an influenza vaccine and spontaneously resolved within 2 days. According to the clinical course, this appeared to be a late-phase immediate hypersensitivity reaction (type I).

Immune responses mediated by CD4+ Th lymphocytes can be either Th1 or Th2 type depending on the profile of cytokines secreted by the Th cells.[7,8] Th1 cells, which produce interferon (IFN)-γ, interleukin (IL)-2, and TNF-α, cause cell-mediated immunity and phagocyte-dependent inflammation.[8] Th2 cells, which produce IL-4, IL-5, IL-9, IL-10, and IL-13, evoke strong antibody responses (including IgE production) and eosinophil accumulation.[8] Most notably, immediate hypersensitivity (type I allergic reaction) is primarily mediated by Th2-mediated mechanisms.[6] Posterior segment intraocular inflammation (PSII) is a putative Th1 dominant autoimmune ocular disorder in which TNF-α is considered to play an important role.[9] In fact, treatment with a TNF-α inhibitor has been shown to improve the visual activity of PSII patients.[9] Furthermore, treatment with this TNF-α inhibitor augmented Th2 activity to help restore proper Th1/Th2 balance in PSII patients.[9] In RA patients, treatment with TNF-α inhibitors, such as etanercept and adalimumab, has been shown to cause atopic dermatitis, which is mediated by Th2 mechanisms.[10,11] These findings are consistent with the antagonism that occurs between Th1- and Th2-mediated pathways.[12,13] In our case, Th2-mediated responses may have been augmented by treatment with etanercept, which is known to strongly suppress Th1 activity, thereby triggering an immediate hypersensitivity response. Fever is a particular prevalent (ca. 6%) adverse event associated with influenza vaccination;[14]

therefore, high fever triggered by the vaccinations may be considered a necessary side effect in RA patients who are undergoing TNF-α inhibitor treatment. In addition, hypersensitivity reaction against the vaccine occurred at the second injection in our case. Therefore, immunologic memory to the vaccine may have been triggered at the first injection before initiation of etanercept treatment. After establishing immunologic memory, immune reaction against the same antigen can augment,[15] and thus more careful attention should be paid to the occurrence of hypersensitivity reaction against the vaccine in patients who have been previously injected with the vaccine during TNF-α blocker treatment.

Hypersensitivity reaction is a type of adaptive immune reaction. Such reactions can be divided into three serial phases: antigen recognition, lymphocyte activation, and the effector phase of antigen elimination.[15] The lymphocyte activation phase includes proliferation (clonal expansion) and differentiation of antigen-specific lymphocytes, and occurs within 4 days of antigen exposure.[15] For example, following immunization with the smallpox virus vaccine, vaccine-specific lymphocytes gradually accumulate and reach their peak level by 14 days after vaccination.[16] According to the time course of adaptive immune responses, the positive D-LST result against influenza vaccine in our case is suggestive of successful immunization, since the test was performed 11 days after vaccine administration. Further, the D-LST finding suggests that antigen-specific lymphocytes recognized the vaccine and is thus also consistent with our opinion that the hypersensitivity reaction was triggered by the vaccine. After all, D-LST (one of the conventional allergic tests) against the vaccine could not distinguish between hypersensitivity and successful immunization in our case. Among the allergic investigations, challenge test against the vaccine may be the most reliable to make clear whether hypersensitivity against the vaccine has occurred; however, the clinical course in our case strongly supported the occurrence of hypersensitivity against the vaccine, and thus the challenge test was considered not to be necessary. Commonly, a diagnosis with hypersensitivity reaction against vaccines may depend on the whole clinical consideration including clinical course, as in our case.

Lastly, further investigations are necessary to clarify whether TNF-α blocker in fact augments Th2 activity, and whether TNF-α blocker actually increases hypersensitivity against influenza vaccine in RA patients. In addition, our patient had a history of allergy to MTX and sulpyrine, and therefore investigation of the susceptibility to hypersensitivity against the vaccine during treatment with TNF-α blocker may be useful.

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