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【 CASE REPORT 】

Elevated White Blood Cell Count and Lactate Dehydrogenase Levels Are Important Markers for Diagnosing Relapse of Adult-onset Still's Disease under Tocilizumab Use

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Abstract:

We encountered a case of refractory adult-onset Still's disease (AOSD) with two relapses. Prednisolone and methotrexate were begun as induction therapy, resulting in the patient's first relapse during tapering of prednisolone. After the introduction of tocilizumab, she achieved remission. However, she experienced a second relapse following prednisolone tapering. While lactate dehydrogenase (LDH) levels and white blood cell (WBC) counts increased in both relapses, interleukin-6 (IL-6) suppression resulted in stable C-reactive protein and ferritin levels in the second relapse. A comparison of the two relapses indicated that increases in both WBC counts and LDH levels can aid in the diagnosis of AOSD relapse.

Key words: adult-onset Still's disease, biomarker, lactate dehydrogenase, relapse, tocilizumab, white blood cell

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Introduction

Adult-onset Still's disease (AOSD) is a rare inflammatory disorder with an unknown etiology. Overproduction of interleukin-6 (IL-6) plays an essential role in the pathogenesis of AOSD (1), and accordingly, tocilizumab (TCZ), a humanized IL-6 receptor antagonist, has been reported as an effective treatment approach for patients with refractory AOSD, secondary to glucocorticoid treatment (2).

C-reactive protein (CRP) is a promising biomarker of AOSD disease activity (1). However, TCZ strongly suppresses CRP production, making the evaluation of disease activity difficult during TCZ treatment in patients with AOSD. Recently, lactate dehydrogenase (LDH) has been identified as a potential biomarker of AOSD relapse (3). The study showed a wide range of changes in LDH levels in patients with relapsed AOSD treated with TCZ, indicating that additional biomarkers for disease activity in patients undergoing TCZ treatment are required.

We herein report a case of refractory AOSD with relapse even after TCZ administration. In this case, the changes in white blood cell (WBC) counts and LDH levels assisted with the diagnosis of relapse during TCZ treatment.

Case Report

An 80-year-old woman was referred to our hospital with a 2-week history of persistent high fever (>39°C), sore throat, arthritis, malaise, and dysphagia. Her medical history revealed gastric cancer (after distal gastrectomy and Billroth I reconstruction), left breast cancer (after left mastectomy and lymph node dissection), and intraductal papillary mucinous neoplasia. Ten days before referral, she had developed an itchy skin rash on her neck. She did not report abdominal pain, nausea and vomiting, diarrhea, or painful urination.

The patient's vital signs included a body temperature of 37.5°C, blood pressure of 104/65 mmHg, pulse rate of 80

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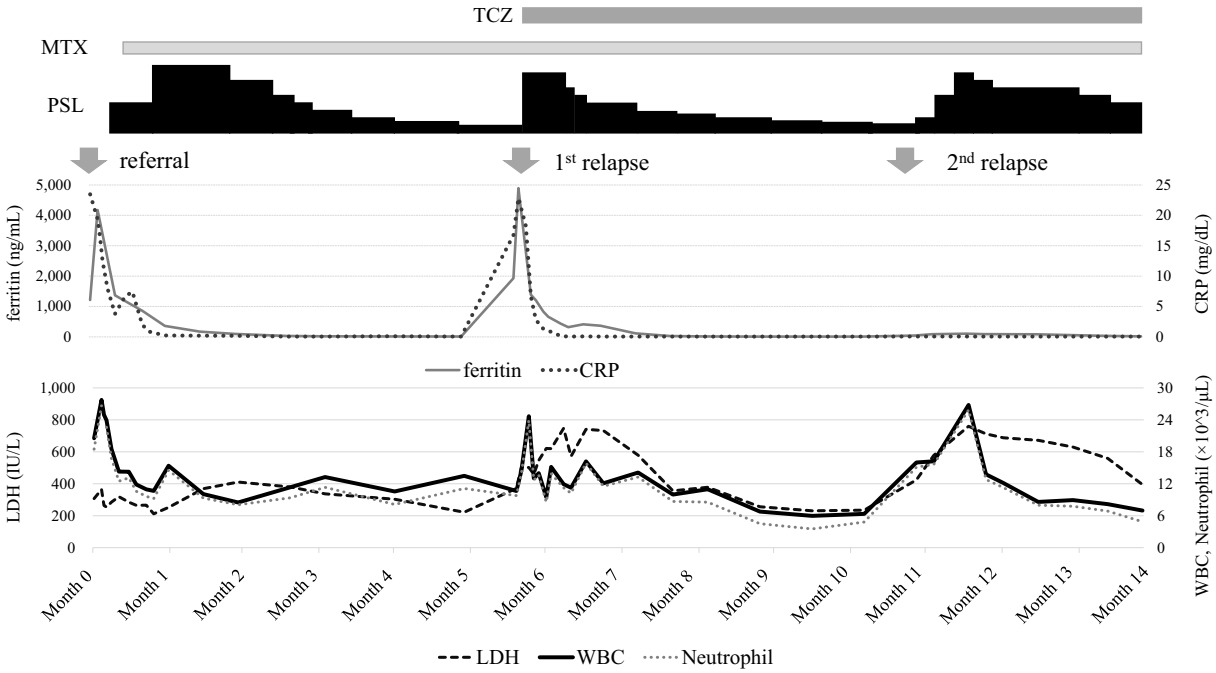

Figure 1. Changes in levels of different biomarkers during treatment of adult-onset Still's disease. Ferritin and C-reactive protein (CRP) levels were markedly elevated during the initial presentation and the first relapse. However, after introducing tocilizumab, the ferritin and CRP levels remained low, even in the second relapse. In contrast, the lactate dehydrogenase (LDH) levels and white blood cell (WBC) count were elevated during both the first and second relapses. However, contrary to LDH levels, the WBC count declined rapidly after treatment enhancement.

beats/min, and peripheral capillary oxygen saturation of 99% on ambient air. A physical examination revealed hepatomegaly (palpable liver 2 cm below the costal margin) and tenderness in the joints of the hands, shoulders, and ankles. Her hand joints were swollen, and a pruritic macular rash was found on the neck of the right precordium. Surgical scars were noted above the umbilicus and the left chest. Heart and lung sounds were clear on auscultation. No petechial hemorrhaging of the eyelids or conjunctiva was observed, and the spleen was not palpable.

Laboratory findings were as follows: WBC count, 20.5×10^3/μL with neutrophil count 18.3×10^3/μL; hemoglobin, 8.5 g/dL; ferritin, 1,173 ng/mL; LDH, 307 IU/L; aspartate aminotransferase, 85 IU/L; alanine aminotransferase, 58 IU/L; total bilirubin, 0.5 mg/dL; γ-glutamyl transpeptidase, 78 IU/L; and alkaline phosphatase, 408 IU/L. Antinuclear antibody, anti-neutrophil cytoplasmic antibody, and rheumatoid factor were negative; blood and urine cultures were also negative. Computed tomography showed no specific findings. Ceftriaxone was administered intravenously as empirical treatment, but the patient's fever persisted. Ultrasonography of the joints indicated synovitis bilaterally. A skin biopsy of the rash showed non-specific findings with eosinophil infiltration.

After excluding the diagnosis of malignancy, infection, and other connective tissue diseases, the patient was finally diagnosed with AOSD according to the Yamaguchi criteria: a fever, arthralgia, and elevated WBC count with neutrophil predominance as the major criteria and a sore throat and liver damage as minor criteria (4). After the diagnosis of AOSD was made, 0.5 mg/kg/day of prednisolone (PSL) was initiated. Because the levels of inflammatory markers did not improve sufficiently (Fig. 1), the dose of PSL was increased to 1 mg/kg, and 4 mg/week of methotrexate (MTX) was also added. The patient's joint pain and neck rash disappeared, and the laboratory test results improved as follows: WBC 10.5×10^3/μL (neutrophil count 8.13×10^3/μL), LDH 303 IU/L, CRP 0.1 mg/dL, and ferritin 14 ng/mL at 4 months after the initiation of treatment. PSL was gradually tapered in the outpatient clinic.

When the PSL dose was reduced to 5 mg/day at 6 months after the initiation of treatment, the patient complained of arthralgia of bilateral wrists. A physical examination showed joint swelling and tenderness of the wrists, and a macular rash was found again on the neck. She was not febrile, and non-steroidal anti-inflammatory drugs did not relieve her symptoms. Laboratory findings showed leukocytosis (WBC 10.6×10^3/μL, with neutrophil count 9.78×10^3/μL), elevated LDH (371 IU/L) and CRP (16.8 mg/dL) levels, and significantly increased ferritin levels (1,929 ng/mL). Computed tomography showed no evidence of malignancy or infection. Two sets of blood cultures were negative. Based on the clinical and laboratory findings, she was diagnosed with a relapse of AOSD, and the dose of PSL was increased to 1 mg/kg/day, along with the administration of 8 mg/kg TCZ every 2 weeks intravenously.

After the initiation of TCZ, she entered remission, with a WBC count of 6.78×10^3/μL (neutrophil count 4.50×10^3/μL), LDH levels 256 IU/L, CRP 0.05 mg/dL, and ferritin 9 ng/mL at 9 months. The PSL dose was tapered to 6 mg/day, but the patient complained of arthralgia of the shoulder joint. A physical examination revealed tenderness of the shoulder joint and a positive painful arc sign, suggesting shoulder arthritis. The patient still had no fever. Laboratory findings showed leukocytosis (WBC: 15.9×10^3/μL, neutrophil count 15.1×10^3/μL) and increased LDH levels (424 IU/L), but the CRP (0.06 mg/dL) and ferritin (42 ng/mL) levels were not increased (Fig. 1). Two sets of blood cultures were negative. Computed tomography showed bilateral pleural effusion but no signs of a tumor or lymph node swelling. Because of her immunodeficient condition and elevated liver function, we also measured cytomegalovirus PP65 antigen, which was negative. The patient was finally diagnosed with AOSD relapse for the second time.

Since she did not achieve remission with 10-20 mg/day PSL, the dose was increased to 1 mg/kg. TCZ was administered at a dose of 8 mg/kg every 2 weeks again. Gradually, her symptoms and laboratory findings improved (WBC 6.97 ×10^3/μL, neutrophil count 4.87×10^3/μL, LDH 395 IU/L, CRP 0.05 mg/dL, and ferritin 16 ng/mL at 14 months). MTX was continued at a dose of 4 mg/week, while PSL was tapered gradually, with no signs of a relapse for 1 year.

Discussion

We encountered a patient with AOSD who had two relapses before and after initiating TCZ treatment. During the second relapse during TCZ treatment, increases in the WBC count and LDH levels were helpful for diagnosing AOSD relapse, since both CRP and ferritin levels remained within the normal limits during this period.

Recently, TCZ has emerged as a promising treatment option for refractory AOSD (5). However, its use in AOSD patients often makes it difficult to make an accurate diagnosis of AOSD relapse. Initially, in the active phase of the disease, there is an increase in the levels of CRP and ferritin; therefore, these parameters are usually monitored to assess disease activity in conventional practice. However, in the present case, the CRP and ferritin levels did not increase during the second relapse of AOSD. This may have been a downstream effect of TCZ, which suppresses CRP, hepcidin, and ferritin via IL-6 and the Janus kinase-signal transducer/activator of transcription (JAK-STAT) pathway (6, 7). CRP, hepcidin, and ferritin are acute-phase reactants, produced mainly in hepatocytes, and are dependent on IL-6 signaling (7). Therefore, clinicians should not rely on CRP or ferritin levels for monitoring disease activity when using TCZ therapy for AOSD.

In contrast, the WBC count and LDH level were helpful biomarkers for monitoring the disease activity of AOSD in our case. Neutrophilia is one of the most prominent clinical characteristics of AOSD (1), and its role in the disease pathogenesis has been well established. Recently, neutrophil extracellular traps have been described as a novel defense mechanism, and their role in connective tissue diseases, including AOSD, has been reported (8). Furthermore, low-density granulocytes, a subset of proinflammatory neutrophils in circulation first discovered in systemic lupus erythematosus, were elevated in patients with active AOSD (9). Pathogen-associated molecular patterns or damage-associated molecular patterns activate multiple cytokine pathways via Toll-like receptors (1). Aside from IL-6, other important cytokines include tumor necrosis factor-α, IL-1, and IL-18 of the inflammasome pathway (10), including neutrophil-derived cytokines (11). The activation of neutrophils is not hampered by IL-6 inhibition because of the upstream pathophysiological pathway, which leads to WBC elevation (Fig. 2).

An earlier observational report described the utility of the change in LDH levels as a biomarker for the disease activity of AOSD under TCZ treatment (3). However, it is a relatively non-specific marker for the inflammatory state because of its wide variation, even in healthy individuals (12). Therefore, an additional biomarker for monitoring the disease activity of AOSD under TCZ treatment is required. During the second relapse of AOSD in the present case, there was an increase in both the LDH level and WBC count by more than two-fold. The combination of WBC counts and LDH levels may thus improve the accuracy of diagnosing AOSD relapse. In elderly-onset adult-onset Still's disease, the WBC count and LDH levels tended to be higher than in younger-onset groups, although the change in the WBC count was not statistically significant (13). WBC count and LDH level elevation was also reported in cases of AOSD relapse in other Japanese case series (3, 14).

LDH is an enzyme that is distributed to nearly all body tissues but is found at higher concentrations in the muscle, liver, kidney, and reticulocytes (11). LDH has five isozymes, named LDH-1 through LDH-5, with different compositions depending on the tissues to which they are distributed (15). For example, the LDH-1 and LDH-2 isozymes are mainly distributed in cardiac muscle, erythrocytes, and kidney, whereas the LDH-4 and LDH-5 isozymes are found primarily in liver and skeletal muscle (12). In our case, we did not measure the LDH isozyme levels. While LDH-4 and LDH-5 were elevated in another previous case report, suggesting liver involvement (16), the diagnostic value of measuring LDH isozymes remains unclear.

PSL causes leukocytosis alone, whereas TCZ decreases the WBC count (17). Since both the WBC count and LDH level are nonspecific biomarkers, it is important to exclude other inflammatory statuses, especially infection, when diagnosing relapse. Immunosuppressive agents, such as PSL and TCZ, can obscure signs and symptoms of infection. In our case, the negative microbiological and radiographical findings and responsiveness to immunosuppressive therapy supported the diagnosis of relapse as well.

Other biomarkers, mainly inflammatory cytokines and

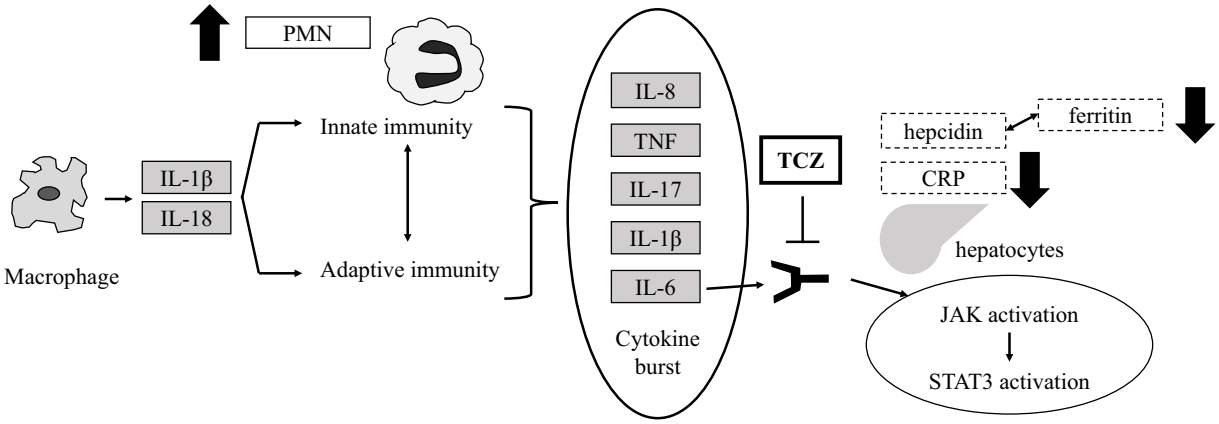

Figure 2. Pathophysiology of adult-onset Still's disease (1, 7). Multiple pro-inflammatory cytokines are involved in the pathophysiology of AOSD. Pathogen-associated molecular patterns or damage-associated molecular patterns activate macrophages and polymorphonuclear neutrophils (PMNs), leading to overproduction of proinflammatory cytokines. Of note, interleukin-6 (IL-6) contributes to the production of acute-phase reactants, such as C-reactive protein (CRP) and hepcidin, in the liver. When tocilizumab is used, IL-6 inhibition stabilizes the CRP levels, even in the active state. However, PMN activation is not hampered by IL-6 inhibition.

chemokines, such as IL-18, have also been shown to be useful in monitoring AOSD (18, 19), but they are not routinely measured in daily clinical practice. Although IL-18 may predict the clinical response to TCZ (20), its use in monitoring of disease activity is not fully understood.

Conclusion

The accurate diagnosis of relapse is often difficult in patients with AOSD undergoing TCZ treatment. Since IL-6 suppression results in stable CRP and ferritin levels, these values cannot be used as dependable biomarkers for monitoring disease activity. As evident from our study, it can be concluded that, in addition to LDH levels, the WBC count is a potential biomarker for the relapse of AOSD after TCZ treatment.

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

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