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【 CASE REPORT 】

Adult-onset Still's Disease during Pregnancy Treated with Tocilizumab

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Abstract:

A 28-year-old woman exhibited a spiking fever, arthritis, and liver disfunction when she was 22 weeks pregnant. She was diagnosed with adult-onset Still's disease (AOSD). As her condition was resistant to corticosteroid therapy, tocilizumab (TCZ) was selected. The TCZ treatment was effective, and she delivered a healthy child while receiving TCZ treatment. Cases in which AOSD first arises during pregnancy are rare, and there have been no reports of TCZ treatment for AOSD being initiated during pregnancy. Although the safety of TCZ treatment during pregnancy has not been established, it may be effective against severe AOSD that develops during pregnancy.

Key words: adult-onset Still's disease, tocilizumab, pregnancy

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Introduction

Adult-onset Still's disease (AOSD) is an inflammatory disorder with an unknown etiology (1). It is characterized by a spiking fever, an evanescent rash, and arthritis (2-5). The first-line therapy for AOSD is high-dose corticosteroids (1, 6, 7). However, some cases are refractory to corticosteroid therapy, and tocilizumab (TCZ), an interleukin 6 inhibitor, has been reported to be useful in such cases (8-10).

AOSD usually affects young adults and women more often than men (1, 11, 12). In addition, some cases involving pregnant women have been reported. Although the relationship between AOSD and pregnancy is unclear, it is rare for AOSD to first arise during pregnancy (13, 14). Although most patients who develop AOSD during pregnancy are treated with corticosteroids, there have not been any case reports about such patients being treated with TCZ.

In our case, refractory AOSD developed during pregnancy. It was difficult to control with corticosteroids alone but was successfully treated with TCZ.

Case Report

In January 2020, a 28-year-old woman developed a fever when she was 22 weeks pregnant. Initially, she was treated symptomatically, but she had a persistent fever of ≥39°C. She was admitted to another hospital at 23 weeks' gestation. Although she was treated with antibacterial therapy (amoxicillin and ceftazidime), her fever persisted. She was transferred to our hospital one week after being hospitalized.

On an examination, she exhibited pharyngalgia and gradually worsening polyarthritis in both her knees and ankle joints. In particular, she had severe polyarthralgia, including heat and swelling, in both knees. She did not develop a skin rash or hepatosplenomegaly during her treatment.

Blood tests revealed the following: white blood cell

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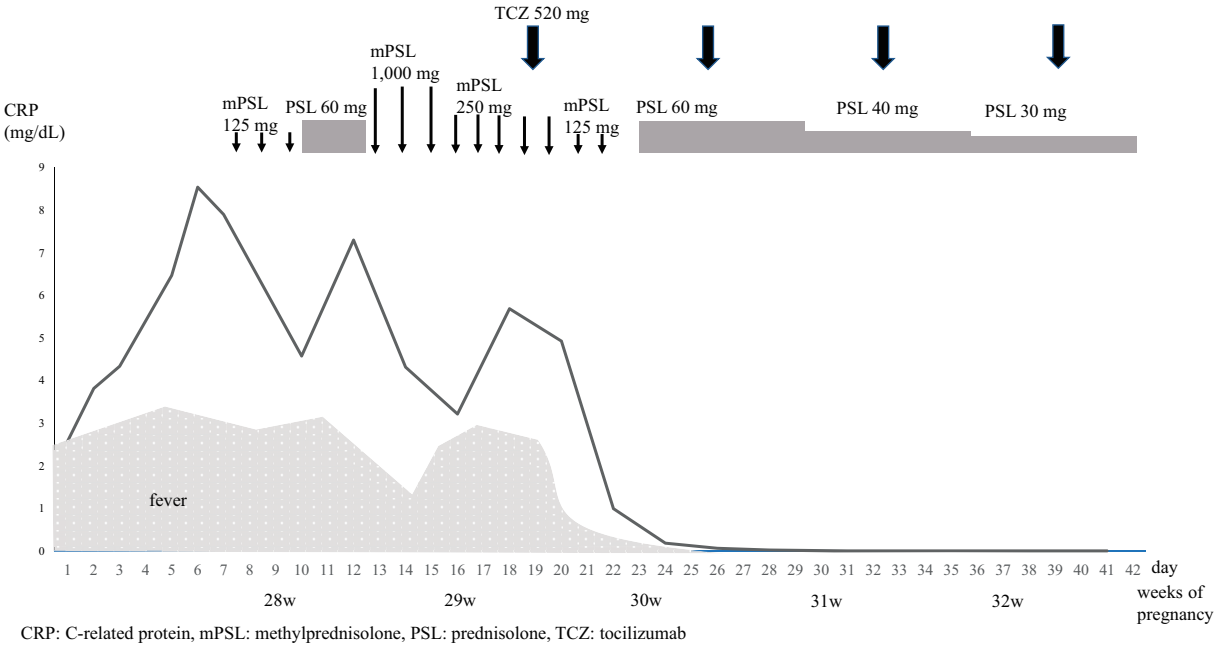

CRP: C-related protein, mPSL: methylprednisolone, PSL: prednisolone, TCZ: tocilizumab

Figure. **The treatment course in this case.**

count: 5,400/μL; hemoglobin: 8.9 g/dL, and platelets: 41.0×10^4/μL. A left shift of her white blood cells was observed. She had liver dysfunction (aspartate transaminase: 142 IU/L, normal: <30 IU/L; alanine aminotransferase: 80 IU/L, normal: <23 IU/L), and a high C-reactive protein (CRP) level (7.90 mg/dL). Her serum ferritin level was also high (2,403 ng/mL, normal: <60 ng/mL). She was negative for autoantibodies, such as antinuclear antibodies, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, myeloperoxidase anti-neutrophil cytoplasmic autoantibodies, and proteinase-3 anti-neutrophil cytoplasmic autoantibodies. Blood, urine, and amniotic fluid cultures were negative. Tests for cytomegalovirus antigenemia; Epstein-Barr virus DNA quantitation; and multiplex polymerase chain reaction (PCR) for herpes simplex viruses type-1 and type-2, cytomegalovirus, and varicella zoster virus produced negative results.

Contrast-enhanced computed tomography revealed no findings that were indicative of an infection, malignancy, lymphadenopathy, or hepatosplenomegaly. No bone marrow test was performed because the patient was pregnant.

Since infection, malignancy, and other collagen-related diseases had been ruled out as causes of the fever, AOSD was diagnosed based on Yamaguchi's classification criteria (15).

The treatment course of this case is shown in Figure. The date of hospitalization is shown in the figure as day 0. We started treatment with methylprednisolone (mPSL, 1,000 mg/day, 3 days) pulse therapy and corticosteroids at 27 weeks and 6 days of gestation. However, the patient's fever persisted after the mPSL pulse therapy, and her CRP level remained elevated. We considered her AOSD to be resistant to corticosteroid therapy. Since the exhaustion caused by her persistent high fever was severe and inflammation persisted, an abortion was considered. However, at that time, she was 28 weeks and 5 days' pregnant (third trimester) and was deemed to be past the organogenesis stage.

Among disease-modifying anti-rheumatic drugs (DMARDs), cyclosporine, tacrolimus, and azathioprine can be used in glucocorticoid-resistant patients and during pregnancy. In addition, TCZ has been suggested to be effective and to have a glucocorticoid-reducing effect, even in patients taking DMARDs (16). In our case, an early therapeutic effect and glucocorticoid reduction were desired, and TCZ was considered useful for these purposes.

Therefore, intravenous TCZ (520 mg, 8 mg/kg) therapy was selected after obtaining the patient's fully informed consent. TCZ was administered once a week according to the dosing regimen for critical cases. After the first dose of TCZ, the patient's fever quickly resolved, and her CRP levels normalized. The prednisolone (PSL) dose was tapered to 15 mg at 36 weeks of gestation, and the same dose was used until delivery. The dosing frequency of TCZ was extended to once every 2 weeks after 38 weeks of gestation.

The patient continued her pregnancy while receiving glucocorticoid medication, and there were no associated complications, such as gestational hypertension or diabetes. There were no problems with the development of the patient's fetus, and she gave birth (via induced labor) at 41 weeks and 1 day of gestation to a boy, weighing 3,192 g with an Apgar score of 8/9. The patient continued receiving TCZ every 2 weeks, and the PSL dose was tapered after delivery without any relapses, including in the perinatal period. Delivery occurred 14 days after the last dose of TCZ had been administered, and the cord blood TCZ concentration, which was analyzed using a commercial enzyme-linked immunosorbent assay [ELISA; tocilizumab ELISA (mAb-based), IG-AB 108; Aybay Tech (Eagle Biosciences, Amherst, USA)], was 256.8 ng/mL. Since maternal and fetal

Table. A Summary of Case Reports of AOSD Onset during Pregnancy from 1971 to Date.

Case	Age	Gestation period at onset (week)	Treatment during pregnancy	Obstetrical complication	Referrence
1	25	NA	Gold	NA	(17)
2	25	6 month	PSL	Neonatal death, prematurity at 28 weeks	(18)
3	19	1st trimester	PSL	None	(19)
4	27	5 month	PSL	Oligohydramnios	(20)
5	30	2 month	PSL	NA	(20)
6	24	5 month	PSL	None	(20)
7	25	8	PSL	None	(21)
8	28	10	Salcylates, IVIg	Pre-eclampsia, placenta abruption, PTD	(22)
9	21	20	PSL, HCQ, AZP	IUGR, PTD	(23)
10	38	22	PSL	None	(23)
11	28	21	PSL, plasma exchange, CyA, DEX	IUGR, PTD	(24)
12	29	12	PSL, anakinra	PTD	(25)
13	33	10	PSL	PPRM, PTD	(26)
14	27	14	PSL, IVIg	PPRM, PTD	(26)
15	36	14	PSL	None	(26)
16	32	22	PSL	PTD	(27)
17	25	26	PSL	NA	(28)
18	32	14	PSL, LCAP	PPRM, PTD, IUGR	(29)
19	38	12	PSL, IVIg	PTD	(13)
20	33	27	mPSL, IVIg	None	(30)
21	28	12	PSL, AZP	None	(14)
Present case	28	22	mPSL, PSL, TCZ	None	

AZP: azathioprine, CyA: cyclosporine, DEX: dexamethasone, HCQ: hydroxychloroquine, HLH: hemophagocytic lymphohistyoyctosis, IUGR: intrauterine growth restriction, IVIg: intravenous immunoglobulin, LCAP: leucocytapheresis, mPSL: methylprednisolone, PPRM: preterm premature rupture of membranes, PSL: prednisolone, PTD: pre-term delivery, TCZ: tocilizumab

samples could not be collected, maternal and fetal blood TCZ concentrations could not be determined. After delivery, both the mother and infant progressed well without any apparent adverse events and did not become susceptible to infection. However, the long-term effects of TCZ on pregnant women and their infants are still unknown, so pregnant women treated with TCZ and their infants should be followed carefully.

Discussion

The relationship between the development of AOSD and pregnancy remains unclear. In addition, cases of AOSD in which the onset occurs during the perinatal period are rare. A summary of reported cases of AOSD from 1971 onwards in which the onset occurred during the perinatal period is shown in Table (13, 14, 17-30). Of the 22 patients, including the present patient, 20 (90.9%) were treated with corticosteroids. Four (18.2%) patients were treated with intravenous immunoglobulins; 2 (9.1%) were treated with azathioprine; and one each was treated with gold, salicylate, hydroxychloroquine, cyclosporine, anakinra, and leukocytapheresis. Regarding obstetric complications, pre-term delivery and intrauterine growth restriction were frequently reported. However, there were no reports of cases that were treated with TCZ during pregnancy. In our case, AOSD occurred at 22 weeks' gestation, TCZ treatment was started at 28 weeks, and a healthy baby was delivered at full term.

Currently, TCZ is recommended for women who are or may be pregnant only when the benefits of treatment outweigh the risks. Some retrospective studies and analyses have not found increased rates of spontaneous abortion or malformations after exposure to TCZ (31, 32). Saito et al. reported a study of umbilical cord blood TCZ concentrations after perinatal TCZ treatment (400 mg every 4 weeks) in pregnancies complicated by AOSD (33). In the latter study, on average, the last dose of TCZ was administered 27 days before delivery, the mean maternal serum TCZ concentration at delivery was 4,893.2 ng/mL, and the mean cord blood concentration was 682.9 ng/mL (about 1/7 of the maternal blood concentration). Based on these findings, they suggested that TCZ may be safe for both mother and child to receive during both pregnancy and breastfeeding because of its low degree of transplacental transmission and the fact that only low levels of TCZ are present in breast milk (33). In our case, the number of days between the administration of the last TCZ dose and delivery was shorter than that reported by Saito et al. (33). However, no major abnormalities in fetal development have been observed, and breastfeeding was continued after delivery on consultation with the patient.

Since there is still limited information on pregnancy outcomes in women exposed to TCZ during pregnancy, the indications for TCZ should be carefully considered. However,

in refractory cases, such as our own, TCZ can be an important option for ensuring the safety of both the mother and fetus. The accumulation of further cases is necessary.

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

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