Adult-onset Still's disease in pregnancy: case report and literature review

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Background: Adult-onset Still's disease (AOSD) is a clinical syndrome whose etiology and pathogenesis remain unclear. The clinical symptoms of AOSD mainly include fever, erythema, arthralgia and muscle pain, which cannot be diagnosed by specific auxiliary examination and can initially attack during pregnancy. The identification of the disease is revealed by a diagnosis of exclusion. Currently, the relationship between pregnancy and AOSD remains unclear. Here, we report on one case of AOSD during pregnancy that was admitted to the Beijing Anzhen Hospital affiliated to Capital Medical University. A 24-year-old woman was admitted to hospital due to intermittent fever, a history of pain and swelling of the large joints at 33 weeks gestation. After the diagnosis of AOSD, the symptoms relieved with medication. The patient delivered a premature, 3450 g baby successfully. Conclusions: The diagnostic criteria of pregnancy complicated by AOSD mainly depends on a diagnosis of exclusion. The literature both at home and abroad shows that the onset of AOSD is closely related to pregnancy, and that pregnancy is one of its predisposing factors. Its clinical manifestations are arthritis, arthromyalgia, fever, pharyngitis and so on, which involve multiple systems. There is no highly specific approach available in the laboratory examination and imaging for this disease.

Keywords
Adult-onset Still's disease; AOSD; Pregnancy

1. Introduction

Adult-onset Still’s disease (AOSD) is a rare, inflammatory disease of unknown etiology in which life-threatening pulmonary and cardiac complications can occur; it generally affects young adults and requires immunosuppressive treatment. The identification of the disease is revealed by a diagnosis of exclusion, which easily leads to misdiagnosis and delayed treatment. AOSD can be triggered by pregnancy. Case reports of the diagnosis of AOSD during pregnancy are even rarer than those in nonpregnant patients. Because these symptoms, including fever and erythema, are often seen in pregnancy and are not specific for a diagnosis of AOSD, this makes the diagnosis and treatment of the disease in obstetrics cases clinically difficult. Moreover, further research is needed on the treatment methods of patients during pregnancy and their impact on maternal and infant outcomes. Herein, we report on one case of AOSD during pregnancy and discuss it in the context of a supporting literature review.

2. Method

Herein, we report on one case of AOSD during pregnancy that was admitted to the Beijing Anzhen Hospital affiliated to Capital Medical University on December 2017. The subject gave the patient informed consent for inclusion before she participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Beijing Anzhen Hospital affiliated with Capital Medical University (NO: 2017036X). In addition, we discuss the case in the context of a supporting literature review. We searched in the PubMed from 1887 to 2018, using keywords “adult-onset Still's disease”, “adult Still's disease, Still's disease” and “AOSD” in combination with “pregnancy”. From among these titles, 20 published full-text English-language articles, including 30 cases, were identified for inclusion important case reports, original articles and review articles, were extensively reviewed by the authors.

3. Case report

A 24-year-old pregnant woman, 33 weeks gestation, was admitted to our hospital due to intermittent fever for 10 days, and a history of pain and swelling of the large joints for 4 days. She began to experience cough, sore throat, and fever, after catching a cold, and the highest temperature recorded for this patient was 38 °C. Symptoms were relieved after rest and physical cooling. She also suffered elbow, wrist, shoulder-joint, and knee-joint swelling pain from 4 days prior to admission. Both lower limbs exhibited edema and the pain had gradually increased, with only limited walking possible, and accompanied by a body temperature of 38.4 °C. Erythrocyte sedimentation rate was 66 mm/h, leukocytes were 13.9 G/L, neutrophilic granulocyte percentage was 91.6%, C-reactive protein (CRP) was 176 mg/L. Body temperature rose to 39.2 °C. Subsequently, erythematous maculopapular rash appeared over the cheek, abdomen and back. Multi-disciplinary consultation considered such patients on admission as presenting with “connective tissue diseases, and adult-onset Still’s disease”. After admission, physical examination revealed the following: erythematous maculopapular rash on cheeks, abdomen, and on the back and outside of the thighs; no subcutaneous bleeding; no exudation; no skin itching;
no enlargement of the superficial lymph nodes of the whole body; swelling of the left eyelid, but no swelling of the finger joints of either hand, or swelling of the bilateral shoulder and knee joints, but swelling of both lower limbs; and limited movement. Breathing sounds were clear in both lungs. Fetal size was appropriate for gestational week 33, and showed a fetal heart rate of 140 bpm. Chest B-mode ultrasonography showed a small level of effusion in the left thoracic cavity of approximately 0.8 cm. Furthermore, the sound transmission was poor, and the consolidation of the lung apex was seen in the left chest cavity. The abdominal ultrasound scan of the kidney showed an enlarged spleen. The total 24-h urinary protein was 418.30 mg, erythrocyte sedimentation rate (ESR) was 100 mm/h, pro-calcitonin was 0.69 ng/mL, D-dimer was 630 ng/mL, the blood was negative for the presence of the rheumatoid factor and anti-streptococcin O (ASO), and both CMV-DNA (Cytomegalovirus, CMV) and EBV-DNA (Epstein-Barr Virus, EBV) were negative. She was given low molecular heparin at 0.6 mL qd ih, methylprednisolone at 16 mg tid po, hydroxylchloroquine sulfate at 0.2 g bid po, and calcium D at 0.6 g qd po. Despite this therapeutic regimen, she still presented with fever (body temperature usually peaked for about 1 h at night). The highest body temperature recorded after admission was 38–38.5 °C, and the rash markedly disappeared greatly when the fever was seen. The fetal heart rate was 180–190 bpm during fever. All of her symptoms, including fever, improved after treatment. The patient delivered a premature baby after labor naturally on 15 December 2017. The Apgar score was 10-10-10, with the weight of the newborn recorded at 3450 g, and the length was 50 cm. After follow-up, the patient subsequently presented with no fever, joint pain, swelling or other discomfort after delivery, and continued therapy with methylprednisolone, hydroxylchloroquine sulfate and other drugs, in addition to follow-up in the rheumatology and immunology department to adjust the drug doses as needed. The types and dosages of the drugs she takes are constantly being adjusted. The patient is in good condition and has no adverse symptoms.

Neonatal examination: The whole body showed membranous skin shedding. The trunk showed scattered erythematous maculopapular rashes with some white secretions, and breathing via both lungs sounded thick, and occasionally large vesicles could be heard. The breathing rate was 40/min, with a strong heart sound, a heart rate of 130 bpm, and no murmur evident. Neonatal blood routine: white blood cell count (WBC) = 35.5 G/L; neutrophil ratio (NE) = 58.9%; hemoglobin (HGB) = 229.1 g/L; platelet (PLT) = 198.0 G/L; and C-reactive protein (CRP) = 3.00 mg/L. The newborn was transferred to our Department of Pediatrics due to suspected infection. Follow-up of a neonatal diagnosis of hemophagocytic syndrome at the Capital Institute of Pediatrics was also selected. The newborn continues to be treated with oral administration of methylprednisolone at 1.0 mg qd, and remains in good condition.

4. Discussion
4.1 Pathogenesis and clinical manifestation of AOSD

Adult-onset Still's disease (AOSD), which was first reported in 1887 [1], is defined as a systemic inflammatory disorder of unknown aetiology and is classified as a multigene autoimmune inflammatory disease. So far, the etiology and pathogenesis of the disease remain unclear. The levels of serum interleukin (IL)-6, IL-8, IL-18, IL-1, tumor necrosis factor (TNF), interferon (IFN), soluble IL-2 receptor and macrophage colony-stimulating factor (M-CSF) are elevated, which results in fever, rash, arthralgia and increased ferritin levels in the blood. There is a positive correlation between the serological levels of IL-18 and the degree of disease activity [2]. Clinical manifestations of AOSD include the following: ① Onset: Fever and rash are the most common symptoms of onset, and fever, rash, and arthralgia are secondary symptoms. Body temperature can drop to normal levels spontaneously by the next morning without any anti-pyretic therapy. ② Transient erythema: Erythema can occur that varies with body temperature. It may be millet-like or accompanied by scratching, usually located on the face, trunk, and limbs, and can also manifest as maculopapules. ③ Arthritis: Almost all patients have joint pain, and about 90% of patients have arthritis. If the cartilage and bone of the involved joints have erosive damage, joint stiffness and deformity may occur in the later stages of the disease. Additionally, about 80% of patients present with muscle pain. ④ Pharynx pain: most patients have pharyngeal pain in the early stages of the disease, sometimes during the whole course of the disease, but which might be reduced after a fever. Pharynx swab-culture is negative and antibiotic treatment is ineffective. Moreover, pharynx pain can be improved with the primary treatment. Others: Some patients have peripheral lymph node enlargement, hepatosplenomegaly, abdominal pain, pleurisy, etc. In rare cases there might be kidney damage, central nervous system abnormality, and peripheral nerve damage. It is additionally not uncommon for a small number of patients to be seen with acute respiratory failure and congestive heart failure, as well as disseminated intravascular coagulation (DIC). The clinical manifestations of the patient we reported were in accordance with the above-mentioned criteria defined in ① through ④ above - and these were seen in addition to splenomegaly, and pleural effusions.

4.2 Laboratory examination

(1) Routine blood tests: in the active phase of the disease, the neutrophil count is elevated in more than 90% of patients, which could be associated with orthochromocyte anemia, with almost all patients presenting with a rapid increase in ESR. (2) The liver enzyme levels i.e., Alanine aminotransferase (ALT), and Aspartate aminotransferase (AST) increase slightly in some patients, especially in cases of fever. (3) Blood bacteria culture is negative. (4) Rheumatoid factor (RF) and antinuclear antibody (ANA) are negative, and only a few individuals show a slightly positive outcome with normal or high complement levels. (5) The level of serum ferritin (SF)
is also significantly elevated, which is helpful for differential diagnosis. We found that the level of SF was positively correlated with the activity of the disease. (6) The leukocytes in the hydrothorax show inflammatory changes, in which neutrophils are increased predominantly. (7) The ESR is shown to increase. (8) Bone marrow examination shows infectious foci.

4.3 Diagnostic criteria and differential diagnosis

AOSD is a diagnosis of exclusion; however, there is no uniform diagnostic standard. At present, the Yamaguchi criteria are widely used [3]. The main indices of these criteria include the following: (1) Temperature at or above 39°C that lasts for more than 1 week; (2) arthralgia that lasts for more than 2 weeks; (3) typical skin rash; and (4) WBC counts of up to or above 10.0 × 10⁹/L, including neutrophil counts of up to or above 0.80. Secondary indices include the following: (1) pharyngalgia; (2) lymph node enlargement and/or splenomegaly; (3) abnormal liver function; and (4) negative rheumatoid factor (RF) and antinuclear antibody (ANA) levels. The above indicators can be diagnosed as AOSD when more than five items are present (two or more of the main indicators are required), excluding infectious diseases (especially septicemia and infectious mononucleosis), malignant tumors (especially malignant lymphoma and leukemia) and other rheumatic diseases (especially multiple aneurysms, rheumatic vasculitis of extravascular signs). Although the level of SF is associated with disease activity, it has not yet been included in the diagnostic criteria. On the basis of adding the Yamaguchi criteria and serum ferritin (i.e., levels above 1250 ug/L) as conditions for the diagnosis of AOSD, its specificity increases from 92.1% to 99.2% [4].

4.4 Treatment

At present, treatments are divided into drug therapy and surgical treatment.

(1) Drug therapy: there is no radical cure for AOSD. Drug therapy can improve clinical symptoms; commonly used agents include non-steroidal anti-inflammatory drugs, glucocorticoids, anti-rheumatics such as methotrexate, gold preparations, azathioprim, and cyclosporine A. Still controversial are the use of some Chinese herbal preparations, and the use of intravenous injection of gamma globulins. Plasma exchange is also a treatment option for AOSD. In recent years, it has been reported that antagonists of IL-1, IL-6 and TNF-α have been used in the treatment of these patients. Reports suggest that the clinical symptoms of the patients can be relieved rapidly [5].

(2) Surgical treatment: patients with arthritis as the main manifestation should have regular X-rays taken of the involved joints. With joint erosion, destruction or deformity, the patients need to consider arthroplasty in the case of extensive joint damage, but is often prevented by early intervention with immune modulating medications.

4.5 Relationship between AOSD and pregnancy outcome

Limited studies have shown that when AOSD presents in pregnancy, the onset is most likely to occur in the mid-trimester of pregnancy, next in early pregnancy, and even less likely post-partum. The risk of pregnancy complications and adverse pregnancy outcomes in patients with AOSD in relative remission are lower than those found in those patients without effective control of the disease. To some extent, AOSD affects pregnancy outcomes; the adverse outcomes of pregnancy include including preterm labor, fetal growth restriction (FGR), premature rupture of membranes, oligohydramnios, and preeclampsia [6]. However, based on few studies and case reports, little is actually known about the pregnancy outcome and neonatal outcome of AOSD patients with pregnancy, especially the impact of different medications during pregnancy on them. In particular, Anna Lin et al. [7] reported case of neonatal hemophagocytic syndrome associated with maternal AOSD for the first time in 2016. The infant they reported was seemingly normal apart from mild prematurity at birth. Later, the infant showed symptoms including high fever, hepatosplenomegaly, cytopenia, marked hyperferritinaemia, hypofibrinogenenaemia, and fulfilled the diagnostic criteria of hemophagocytic syndrome. The author pointed out that the infants present with clinical features mimicking severe sepsis or pneumonia typically. However, they have negative microbial cultures and are unresponsive to anti-microbial agents. Although the exact mechanism cannot be fully elucidated, it is likely that the infants acquired secondary hemophagocytic syndrome via vertical transmission of factors from her mother with AOSD. Researchers thought that neonatologists should be reminded of the possibility of hemophagocytic syndrome for newborns with family history, symptoms such as fever, hepatosplenomegaly and cytopenia and no response to antimicrobial drugs. Isolation, prevention and corticosteroid treatment and chemotherapy are important treatment options [7].

Different patients show diversity and heterogeneity in the course of the disease. Most patients are prone to recurrent attacks after remission, and a few do not relapse after a single remission and have a tendency of self-limitation. Some patients exhibit the chronic persistent-activity type, which eventually appears as a chronic arthritis with accompanying cartilage and bone destruction similar to that seen in rheumatoid arthritis.

4.6 Retrospective analysis

As described in the initial 1982 case report, AOSD can be triggered by pregnancy. We collected 31 cases of AOSD during pregnancy (Table 1), involving women aged 19–40 years (Median age = 28.5), with the majority of pregnant patients with AOSD occurring at 8 to 26 weeks of gestation and during the postnatal period. However, the case at our hospital was diagnosed for the first time at 33 weeks of gestation. In terms of symptoms and laboratory tests, the main manifesta-
| Case no. | Study                        | Age | Time of pregnancy (wg) | AOSD features | Ferritin levels/GF | Treatment | AOSD outcome during the pregnancies | Adverse obstetrical outcome |
|---------|------------------------------|-----|------------------------|---------------|-------------------|-----------|---------------------------------|-----------------------------|
| 1       | Bywaters, 1971 [1]           | 34  | -                      | F, AM, E      | NA                | Gold      | -                               | Not satisfactory             |
| 2       | Kaplinsky, 1980 [8]          | 34  | -                      | A, F, L, E    | NA/NA             | Aminopyrine, gold salt | Polycyclic (PP) | None                             |
| 3       | Green, 1982 [9]              | 23  | 25                     | A, F, HSMG, L, E | NA/NA             | NA        | Polycyclic                       | Neonates death, (28, wg, PP) prematurity at 28 wg |
| 4       | Yebra Bango, 1985 [10]       | 19  | 12                     | A, F, HSMG, E, Pha | NA/NA             | Prednisone | Polycyclic                        | Neonates death, (28, wg, PP) prematurity at 28 wg |
| 5A      | Katz, 1990 [11]              | 32  | PP2w                   | E, A          | NA/NA             | NSAID     | Polycyclic                       | None                         |
| 5B      | Katz, 1990 [11]              | 35  | PP2m                   | F, E          | NA/NA             | Prednisone 40 mg/d | -                               | Not satisfactory             |
| 6       | Leff, 1990 [12]              | 23  | PP                     | F, A, E       | NA/NA             | Prednisone 20 mg/d | -                               | Not satisfactory             |
| 7A      | de Minguel et al., 1992 [13] | 38  | PP3m                   | F, A, E       | NA/NA             | Prednisone 30 mg/d/AZA | -                               | Satisfactory                 |
| 7B      | de Minguel et al., 1992 [13] | 40  | PA                     | -             | NA/NA             | MTX       | -                               | Fetal loss                  |
| 8A      | Le Loet, 1993 [14]           | 27  | 20                     | A, F, L, E, Pha | NA/NA             | Prednisone 1 mg/kg/d | Polycyclic                       | OHA                         |
| 8B      | Le Loet, 1993 [14]           | 24  | 20                     | A, F, L, E, Pha, AM | NA/NA             | Prednisone 20 mg/d | Polycyclic                       | None                        |
| 8C      | Le Loet, 1993 [14]           | 24  | PP                     | E             | NA/NA             | Prednisone 10 mg/d | -                               | IUGR                        |
| 9       | Falkenbach, 1994 [15]        | 25  | 8                      | A, F, L, AM, HSMG, S, Pha | NA/NA             | High dose prednisone, EDX | Polycyclic (suites de couches) | FE                          |
| 10      | Liozon, 1999 [16]            | 28  | 10                     | A, F, L, E, Pha | NA/NA             | NA        | Polycyclic (22 wg, 31 wg, PP 5 m) | Pre-eclampsia               |
| 11A     | Vivien, 2003 [17]            | 21  | 20                     | F, AM, L, S, Pha, E | NA/NA             | Prednisone 1 mg/kg+HCQ | Polycyclic (23 wg, PP) | Prematurity at 34 wg, IUGR |
| 11B     | Vivien, 2003 [17]            | 38  | 22                     | A, F, E       | NA/NA             | Prednisone 1 mg/kg/d | Monocyclic                       | None, 41 wg birth            |
| 11C     | Vivien, 2003 [17]            | 21  | 20                     | F, A, Pha     | 33900/NA          | Prednisone 0.5 mg/kg/d | Monocyclic                       | IUGR, Prematurity at 34 wg |
| 12A     | Mok et al., 2004 [18]        | 30  | 17                     | AM, E         | 3985/NA          | Prednisone 5 mg/kg/d/HCQ | -                               | IUGR                        |
| Case no. | Study                  | Age | Time of pregnancy(wg) | AOSD features | Ferritin levels/GF | Treatment                      | AOSD outcome during the pregnancies | Adverse obstetrical outcome |
|---------|------------------------|-----|-----------------------|---------------|-------------------|--------------------------------|------------------------------------|------------------------------|
| 12B     | Mok et al., 2004       | 27  | 21                    | F, AM, E      | NA/NA             | Prednisone 60 mg/kg/d          | -                                  | Not satisfactory              |
| 12C     | Mok et al., 2004       | 22  | PP                    | AM            | NA/NA             | NSAID                          | -                                  | IUGR                         |
| 13      | Fischer-Betz, 2011     | 29  | 12                    | F, A, HSMG, E, Pha | > 40000/NA       | Prednisone 100 mg/d, Anakinra  | Polycyclic                        | Prematurity at 36 wg          |
| 14      | Yamamoto, 2011         | 28  | 21                    | F, E, A, AM, L, S, HLH | 24883/NA      | Methylprednisone, Cyclosporine | Monocyclic                        | Prematurity at 33 wg, IUGR     |
| 15      | Hammami, 2013          | 32  | 22                    | F, A, E, AM, SMG, S | 12957/NA      | Prednisone 1 mg/kg             | Monocyclic                        | Prematurity at 34 wg          |
| 16      | Mahmoud, 2014          | 25  | 26                    | F, A, pancytopenia | 1733/NA       | Prednisone 60 mg/J            | Monocyclic                        | NA                           |
| 17A     | Gerfaud-Valentin, 2014 | 33  | 10                    | F, A, E        | 3592/1%        | Prednisone 0.7 mg/kg/d         | Flare at 1 month PP, polycyclic course | Prematurity at 34 wg, PPRM   |
| 17B     | Gerfaud-Valentin, 2014 | 27  | 14                    | F, A, SMG, E  | 4124/12%       | Prednisone 1 mg/kg/d+lg IV     | Flare at 1 and 3 mo, polycyclic   | None                         |
| 17C     | Gerfaud-Valentin, 2014 | 36  | 14                    | F, AM, E, L   | 13111/12%      | Prednisone 0.5 mg/kg/d         | Monocyclic                        | Prematurity at 32.5 wg, PPRM, OHA |
| 18      | Tsuyoshi, 2015         | 32  | 14                    | F, L, A, E, Pha | 2920/NA       | Prednisone 1 mg/kg/d, LCAP     | Monocyclic                        | Prematurity at 34 wg, PPRM    |
| 19      | Plaçais, 2016          | 38  | 12                    | F, HSMG, A, Pha | 41000/< 5%     | Prednisone 1 mg/kg/d, IV Ig    | Polycyclic                        | Premature at 34 wg, fetal extraction |
| 20      | Anna Lin, 2016         | -   | 32                    | F, E, AM, L, HSMG | NA/NA       | Systemic corticosteroids        | -                                 | Premature at 35 wg, Neonatal hemophagocytic syndrome |
| 21      | Smith et al, 2018      | 30  | -                     | -              | NA/NA          | Anakinra 100 mg/d, Prednisone 60/30 mg/d | -                                 | None, Neonatal jaundice       |

Wg, weeks of gestation; A, arthritis; E, erythema; F, fever; L, lymphadenopathy; S, seritis; AM, arthromyalgia; FE, fetal extraction; Pha, pharyngitis; OHA, oligohydroamnios; SMG, splenomegaly; HSMG, hepatosplenomegaly; IUGR, intrauterine growth restriction; LCAP, leucocytapheresis; PPRM, pre-term premature rupture of membranes; IV Ig, intravenous immunoglobulins; PP, post-partum; PA post-abortion.
tions were arthritis, arthromyalgia, fever, and pharyngitis, among other observations. The serum ferritin level was between 1311 and 40000 ng/mL. There may be some increased risk for adverse pregnancy outcomes, as shown in these few studies; the patient in the present report eventually gave birth prematurely. Of the 31 cases mentioned above, there were 11 cases of premature labor, 3 cases of premature rupture of the membranes, 6 cases of intrauterine fetal growth restriction, 2 cases of oligohydramnios, 1 case of neonatal death and 1 case of abortion. Of the 11 cases of premature labor, 10 were treated with steroids during pregnancy. The patient admitted to our hospital was also treated with steroids during pregnancy and delivered a premature baby at 36 weeks of pregnancy. The relationship between the occurrence of complications and the specific pathology of AOSD is unclear; it might be associated with steroid therapy and side-effect manifestations. However, recent studies have shown that high levels of IL-18 during pregnancy might provoke onset of potential diseases, leading to the occurrence of AOSD [20]. In terms of treatment regimen, most of the patients received hormonal therapy, two of them were treated with intravenous immunoglobulin, and there was no significant difference between monocyclic and polycyclic outcome [26]. In the future, AOSD pathophysiology and the application of targeted therapy may benefit patients and obtain a remarkable curative effect [23]. As mentioned earlier in the article, hemophagocytic syndrome may also be one of the manifestations of adverse neonatal outcomes. As we reported in this case, the neonates delivered by pregnant women with AOSD should be alert to the occurrence of hemophagocytic syndrome.

In conclusion, the diagnostic criteria of pregnancy complicated by AOSD remain unclear, and mainly depend on a diagnosis of exclusion. Due to a diverse clinical manifestation of AOSD, there is a high rate of clinical misdiagnosis. The literature both at home and abroad shows that the onset of AOSD is closely related to pregnancy, and that pregnancy is one of its predisposing factors. Its clinical manifestations are arthritis, arthromyalgia, fever, pharyngitis and so on, which involve multiple systems. There is no highly specific approach available in the laboratory examination and imaging for this disease. AOSD is a group of rare clinical syndromes, and at present, very little is known about the mechanism relating pregnancy to AOSD.

Finally, the prognosis for the pregnant woman and her fetus, as well as adequate follow-up of the pregnancy and postnatal period, collectively, present us with a great deal of uncertainty. A significant program of published clinical and basic research are still needed in order to reduce this uncertainty and strengthen a more specific differential diagnosis in the future.

Author contributions

KFW and CL conceived and designed the study. JL consulted the literature. CL wrote the paper. KFW and JL reviewed and edited the manuscript. All authors read and approved the manuscript.

Ethics approval and consent to participate

The subject gave the patient informed consent for inclusion before she participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Beijing Anzhen Hospital affiliated to Capital Medical University (NO:2017036X).

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Conflict of interest

The authors declare no competing interests.

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