Case Report

Second-trimester miscarriage caused by recurrent *Klebsiella pneumoniae* infection: a case report

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Background: *Klebsiella pneumoniae* (*K. pneumoniae*) can cause hospital- and community-acquired pneumonia, and urinary tract, wound, and blood infections. As there are few reports on *K. pneumoniae* infections in pregnancy and no treatment guidelines, diagnosis and treatment are difficult. The diagnosis and treatment require a bacterial culture to confirm the diagnosis. Therefore, the condition is often exacerbated due to a lack of timely medication.

Case Description: We report a case of a pregnant woman with recurrent *K. pneumoniae* infection during pregnancy. The 40-year-old woman was admitted to hospital at 14 weeks gestation due to fever of unknown origin. She was treated with empiric antibiotics, and her fever resolved within 1 day. A blood culture showed *K. pneumoniae* infection. She was discharged after 11 days of treatment. However, 10 days later, she was re-hospitalized due to fever, and treated with cefoperazone sodium and sulbactam sodium. Her fever resolved within 1 day. A blood culture again showed *K. pneumoniae* infection. On day 5, she experienced chills and a miscarriage. Cervical secretions showed *K. pneumoniae*, and a placental examination revealed chorioamnionitis. The treatment was changed to meropenem, and the patient recovered within 2 weeks.

Conclusions: When a fever of unknown origin occurs during pregnancy, one should be wary of *K. pneumoniae* recurrence or secondary infection, and use sensitive antibiotics early. When *K. pneumoniae* is cultivated, the course of treatment must be sufficient, and the source of infection must be actively searched to prevent secondary infections, such as kidney cysts, liver cysts, lung cysts, and community infections. Finding the cause and taking appropriate treatment can prevent the occurrence of adverse pregnancy and childbirth history.

Keywords: *Klebsiella pneumoniae* infection (*K. pneumoniae* infection); pregnancy; acute chorioamnionitis (AC); case report

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Introduction

Bloodstream infections (BSIs) can be caused by various pathogenic microorganisms invading the bloodstream and are collectively referred to as bacteremia and sepsis (1,2). The incidence and mortality of systemic infectious diseases continue to increase progressively. *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) are the main causes of BSIs (3,4). A positive blood culture is defined as the presence of *E. coli* or *K. pneumoniae* in at least 1 blood culture bottle. Patients with *K. pneumoniae* infection tend to have a more marked systemic inflammatory response than patients with *E. coli* infection. However, microbial identification, and subsequent antimicrobial screening, rely on parenchymal cultures such as fetal blood, tissue culture, and placental subchorionic fibrin swabs. Therefore, patients often aggravate their condition due to failure to take the medication in time. To our knowledge, no cases of miscarriage due to recurrent *K. pneumoniae* BSIs have been reported to date. In this article, we report the case of a miscarriage at 19 weeks + 5 days gestation due to a recurrent *K. pneumoniae* BSI associated with acute chorioamnionitis (AC). This reminds us that when fever of unknown origin occurs during pregnancy, we should be vigilant against the recurrence or secondary infection of *K. pneumoniae*, actively search for the source of infection, prevent secondary infection, and take corresponding treatment measures immediately after finding out the cause, which can prevent adverse pregnancy and occurrence of childbirth history. We present the following article in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1334/rc).

Highlight box

Key findings

- We report a case of a pregnant woman with recurrent *K. pneumoniae* infection during pregnancy.

What is known and what is new?

- In recent years, *K. pneumoniae* has become increasingly more drug resistant due to the irrational use of antibiotics, which poses a major challenge to clinical prevention and control.
- The present case provides guidance on how to treat pregnancy complicated by *K. pneumoniae*, how to prevent miscarriage, and how to prevent the formation of drug-resistant bacteria and the production of super bacteria.

What is the implication, and what should change now?

- Further studies need to be conducted to gain an understanding of the virulence of *K. pneumoniae*, and the optimal duration of treatment needs to be determined.

Case presentation

Clinical features and treatment during the first hospitalization

A previously healthy 40-year-old woman with no history of infection, hypertension, diabetes, heart disease, blood transfusion, penicillin allergy, or food allergy underwent an incision of transcervical resection of septum at our hospital in July 2017. In August 2019, she experienced a spontaneous preterm premature rupture of membranes (PPROMs), and thus labor was induced. In May 2022, she was admitted to Second Hospital of Shanxi Medical University with a 2-day history of fever of unknown origin.

On admission, the patient had a temperature of 38.8°C. She had no nausea, vomiting, abdominal pain, diarrhea, low back pain, dysuria, or vaginal bleeding. Her hematology results revealed a white blood cell (WBC) count of 7.99×10^9/L with 93% neutrophils and a hemoglobin level of 113 g/L. Her blood biochemistry results revealed a C-reactive protein (CRP) level of 207 mg/L and a procalcitonin level of 5.78 ng/mL. Her erythrocyte sedimentation rate was 58 mm/hour. The culture of cervical secretions was negative for Group B *Streptococcus* and yielded no growth. The patient was treated with intravenous sulbactam cefoperazone sodium and sulbactam sodium (3.0 g, 8-hourly) as empiric antibiotic therapy. Her body temperature returned to normal after 1 day of treatment (*Table 1*).

On day 3, the patient's body temperature was 36.8 ℃, and her hematology results revealed a WBC count of 7.65×10^9/L, a neutrophil count of 5.76×10^9/L, a hemoglobin level of 97 g/L, and a neutrophil % of 75.3%. Her CRP level had decreased to 122 mg/L, and the blood culture was positive for *K. pneumoniae*. As the organism is sensitive to sulbactam cefoperazone sodium and sulbactam sodium, intravenous antibiotic treatment with sulbactam cefoperazone sodium and sulbactam sodium (3.0 g, 8-hourly) was continued.

On day 5, the patient's body temperature was 37 ℃, and her hematology results revealed a WBC count of 7.5×10^9/L, a neutrophil count of 5.62×10^9/L, and a hemoglobin level of 108 g/L. The antibiotic was changed to cefuroxime (1.5 g, 12-hourly) by intravenous infusion.

On day 12, the patient's body temperature was 36.8 ℃, and her hematology results revealed a total WBC count of 3.54×10^9/L, a neutrophil count of 9.13×10^9/L, a

Table 1 The patient's body temperature and blood test results during her first hospitalization

Parameter	Normal range	Day 1	Day 3	Day 5	Day 12
Body temperature (℃)	36.0–37.0	38.8	36.8	37	36.8
WBC (×10^9/L)	3.50–9.50	7.99	7.65	7.5	3.54
Neutrophils (×10^9/L)	1.80–6.30	7.44	5.76	5.62	9.13
Neutrophil %	40.00–75.00	93	75.3	75	83.9
Hemoglobin (g/L)	115.0–150.0	113	97	108	108
CRP (mg/L)	0.00–4.00	207	122	–	–
Procalcitonin (ng/mL)	0.00–0.51	5.78	–	–	0.9
ESR (mm/hour)	0.00–20.00	58	–	–	–

WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 2 The patient's body temperature and blood test results during her second hospitalization

Parameter	Normal range	Day 1	Day 2	Day 4	Day 5	Day 6	Day 11	Day 16
Body temperature (℃)	36.0–37.0	40.5	38	37.3	37	37.3	36.8	36.9
WBC (×10^9/L)	3.50–9.50	–	9.32	–	–	–	–	4.48
Neutrophils (×10^9/L)	1.80–6.30	–	7.74	–	–	–	–	2.13
Neutrophil %	40.00–75.00	–	83.1	–	–	–	–	47.6
Hemoglobin (g/L)	115.0–150.0	–	85.0	–	–	–	–	105
CRP (mg/L)	0.00–4.00	119.49	184	–	–	–	–	3.04
Procalcitonin (ng/mL)	0.00–0.51	23.43	60.22	–	–	–	–	–
ESR (mm/hour)	0.00–20.00	53	–	–	–	–	–	–

WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

hemoglobin level of 108 g/L, a neutrophil % of 83.9%, and a procalcitonin level of 0.9 ng/mL. The results of the blood culture were negative. Cefuroxime (1.5 g, 12-hourly) by intravenous infusion was continued. The patient recovered completely, with remission of her fever, and a decrease in her CRP level and was discharged on day 12.

Clinical features and treatment during the second hospitalization

Seven days after her discharge, the patient experienced an increase in body temperature to 39 ℃, accompanied by dizziness, fatigue, and generalized myalgia, without gastrointestinal or respiratory symptoms, but had no vaginal bleeding (*Table 2*).

Ten days later, she was admitted to the emergency department with a body temperature of 40.5 ℃. Her blood biochemistry results revealed an ultrasensitive CRP level of 119.49 mg/L, a calcitonin level of 23.43 ng/mL, and an erythrocyte sedimentation rate of 53 mm/hour. An obstetric ultrasound revealed an intrauterine pregnancy with a single live fetus, a mid-gestation hypoplastic placenta, and a uterine fibroid (*Figure 1*). A blood culture revealed gram-negative bacilli (+). A urinalysis revealed urinary ketones 4+. Cefoperazone sodium and sulbactam sodium were administered by intravenous drip.

On day 2 of the patient's second admission, her temperature was 38 ℃. Her hematology results revealed a WBC count of 9.32×10^9/L, an absolute neutrophil count of 7.74×10^9/L, a neutrophil % of 83.10%, and a hemoglobin level of 85.0 g/L. Her blood biochemistry results revealed a calcitonin level of 60.22 ng/mL.

On day 3, the patient's temperature was 37.5 ℃. A rapid fully automated blood culture identified *K. pneumoniae*

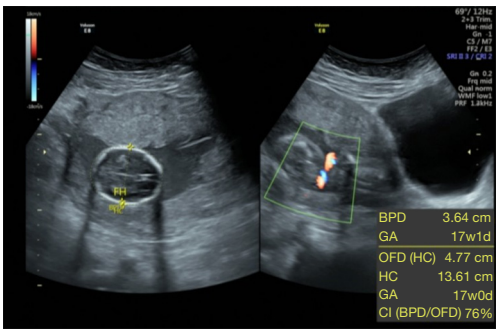

Figure 1 Obstetric ultrasound showing intrauterine pregnancy, a single live fetus, a low-lying placenta in the second trimester and uterine fibroids. BPD, biparietal diameter; GA, gestational age; OFD, occipito-frontal diameter; HC, head circumference; CI, cephalic index.

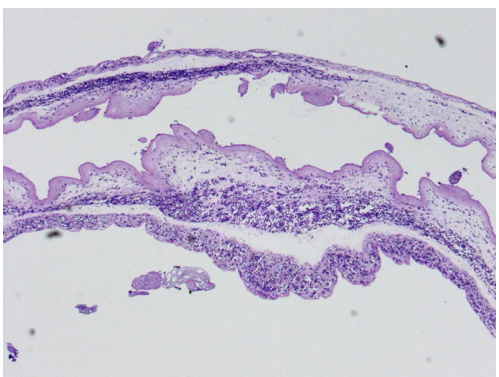

Figure 2 Stage III, grade III chorioamnionitis. Severe AC with focal amniotic necrosis. (Hematoxylin and eosin staining, 10×). AC, acute chorioamnionitis.

sensitive to meropenem, cefazolin, cefuroxime, ceftriaxone, and cefoperazone sodium and sulbactam sodium. The patient continued to be treated with cefoperazone sodium and sulbactam sodium for 2 weeks according to the original protocol. Her temperature and laboratory test results continued to be monitored.

On day 4, her body temperature was normal, but her blood culture was still positive for *K. pneumoniae*, and the results of a routine stool examination were normal.

On day 5, the patient's body temperature was normal. She experienced some vaginal discharge and lower abdominal pain without vaginal bleeding. A blood culture was positive for *K. pneumoniae*, and *K. pneumoniae* was identified in her cervical discharge, but a sputum culture did not reveal any pathogens. The cefoperazone sodium and sulbactam sodium were discontinued and replaced with intravenous meropenem (1 g, 8-hourly). We realized that an abortion was inevitable due to the *K. pneumoniae* infection and performed a pharmacological abortion.

On day 6, the patient's body temperature was 37.3 ℃. She underwent dilation and curettage for incomplete pharmacological abortion, and a dead fetus with a normal appearance was removed. The placenta-fetal membranes were sent for pathological examination. A culture of cervical secretion was negative for group B *Streptococcus*. The intravenous meropenem was continued.

On day 11, the patient's body temperature was normal. The histopathology of the sail-shaped placenta-fetal membrane tissue was consistent with stage III, grade III chorioamnionitis (*Figure 2*). The intravenous meropenem was continued on the advice of a pharmacologist.

On day 16, the patient's body temperature was normal. Her hematology results revealed a WBC count of 4.48×10^9/L, a neutrophil count of 2.13×10^9/L, a neutrophil % of 47.6%, and a hemoglobin level of 105 g/L. Her blood biochemistry results revealed that her CRP level had decreased to 3.04 mg/L.

On day 17, the patient's body temperature remained normal, and the results of the blood culture were negative.

On day 18, the patient's body temperature remained normal. A transabdominal gynecological color ultrasound revealed a uterine fibroid and a uterine cavity effusion. An abdominal ultrasound revealed no significant abnormalities in the liver, gallbladder, pancreas, spleen, or kidneys.

On day 19, the patient's body temperature remained normal. Plain and contrast-enhanced computed tomography (CT) of the abdomen revealed a right renal cyst, but no significant abnormalities of the liver, gallbladder, pancreas, spleen, or left kidney.

By day 20, the patient had recovered completely and was discharged from hospital after completing 14 days of meropenem therapy.

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Medical Ethics Committee of the Second Hospital of Shanxi Medical University (No. 2022YX088). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Materials and methods

We searched the Pubmed database for articles on *K.*

pneumoniae infection in pregnancy without setting any restrictions. The titles and abstracts of the articles were screened to identify the relevant articles. All the relevant articles were obtained in full-text format and additional references were screened.

Discussion

K. pneumoniae is a gram-negative rod-shaped bacterium, with numerous serotypes and strong pathogenicity. Its external features include a thin peptidoglycan layer, thick outer membrane and thick capsule with O antigen and K antigen. Most strains have fimbriae, without spores or flagella (5). *K. pneumoniae* is a common opportunistic pathogen that can cause hospital- and community-acquired infections, including urinary tract infections, respiratory tract infections, and BSIs, purulent liver abscesses (2), sepsis, purulent meningitis, and other critical illnesses with extremely high mortality rates (6). *K. pneumoniae* bacteremia is more common in men, and the most common sources of infection are the abdomen, lungs and liver (7). According to a study by Kuo *et al.* (8), the length of hospital stay and hospitalization costs of patients with *K. pneumoniae* bacteremia are significantly higher than those of patients with *E. coli* bacteremia.

In the present case, the patient's symptoms (of which fever was the first symptom) started in the second trimester of pregnancy, and there were no obvious symptoms to suggest the source of the infection. Due to the patient's pregnancy, some investigations were restricted. The patient's procalcitonin and high-sensitivity CRP levels, and erythrocyte sedimentation rate were all significantly elevated, but her WBC count was not high. Only the neutrophil count and neutrophil % were increased. A blood culture showed *K. pneumoniae* infection. Drug susceptibility testing showed that the isolate was sensitive to cefoperazone sodium and sulbactam sodium and cefuroxime. Due to the patient's sensitivity to cefuroxime, cefoperazone sodium and sulbactam sodium were de-escalated on the 5th day, and the patient was switched to cefuroxime, which was administered for 7 days.

The patient requested to be discharged after 11 days of treatment. During the first hospitalization, the *K. pneumoniae* was a BSI, the only symptom was fever, and the patient did not develop a severe infection. However, the infection focus and the source of infection were not found. Further, it was unclear why the patient's only symptom was fever. In retrospect, we question whether we could have done more to determine the source of infection and to treat it, and whether this could have prevented the patient's miscarriage.

Along with differences in capsular polysaccharides and changes in bacterial virulence, *K. pneumoniae* has also evolved a new variant, hypervirulent *K. pneumoniae* (hvKP) (9). HvKP has unique phenotypic characteristics, such as hyperviscous mucus production and a distinct serotype and genotype (including harboring special virulence genes), is more clinically pathogenic than *K. pneumoniae*, can cause severe community-acquired infections, such as liver abscess, suppurative endophthalmitis, suppurative meningitis, and osteomyelitis, in young individuals with normal immune function, and dissemination can occur to other organs (10). The virulence genes and the multidrug-resistance genes are thought not to overlap in the hvKP genome. Most hvKP strains are highly sensitive to commonly used antibiotics (other than ampicillin), and the rate of drug resistance is extremely low. Thus, the clinical treatment of hvKP infection can be timely and effective (11).

Carbapenems are currently the first-line drugs for the treatment of severe infections caused by multidrug-resistant bacteria producing extended-spectrum β-lactamase (ESBL) and cephalosporinase (AmpC). The detection rate of penem-like *Enterobacteriaceae* (CRE), especially carbapenem-resistant *K. pneumoniae* infection, has been steadily increasing (12,13). The emergence of carbapenem-resistant hvKP, coupled with its high virulence and drug resistance, has led to the creation of a "superbug", which poses a challenge to global public health and antibiotic therapy (14,15). From 2005 to 2018, the bacterial resistance monitoring data of the Chinese Bacterial Resistance Detection Network showed that the resistance rate of Klebsiella pneumonia to imipenem and meropenem increased eightfold, from 3.0% and 2.9% to 20.9% and 24.0%. In recent years, *K. pneumoniae* has become increasingly more drug resistant due to the irrational use of antibiotics, which poses a major challenge to clinical prevention and control. *K. pneumoniae* is particularly resistant to ESBL-producing bacteria. In the past, carbapenems was often used for targeted control; however, in recent years, *K. pneumoniae* has become increasingly resistant to with carbapenem antibiotics (16,17). Thus, alternative antibiotic strategies need to be developed.

Ten days after the patient was discharged from the hospital, there was no obvious cause for the recurrence of fever. The patient's symptoms were the same as those observed during the first hospitalization, except

for headache and myalgia. After admission, the patient underwent various examinations, including routine urine and blood tests, a blood culture, sputum culture, and vaginal secretion culture. Her body temperature returned to normal after the intravenous administration of sulbactam cefoperazone sodium and sulbactam sodium. The symptoms, signs, and tests conducted were the same as those conducted during the patient's first hospitalization. The blood culture was rapidly positive for *K. pneumoniae*, and the therapy of sulbactam cefoperazone sodium and sulbactam sodium was continued. However, on the 5th day of admission, she developed vaginal bleeding and PPROM, making miscarriage inevitable. Additionally, *K. pneumoniae* was cultured in cervical secretions, which indicated that there was *K. pneumoniae* in the fetal environment, which could lead to miscarriage. Thus, the antibiotic was changed to meropenem, and on the 7th day of admission, an abortion was performed, and the placenta was cleared.

The patient was given intravenous meropenem for a total of 14 days after the surgery. The blood culture became negative and her routine blood test results became normal. The only abnormality discovered on the repeat gynecological and abdominal ultrasonography, and pelvic and abdominal CT was cysts in the right kidney. The course of the second hospitalization was similar to the first, except that the infection was more severe, and a miscarriage occurred. The patient's body temperature and routine blood test results had returned to normal, but she developed AC, leading to a miscarriage. It is not known whether the infection was AmpC-resistant or whether it was due to a more virulent strain of *K. pneumoniae*, as the source and focus of infection were not found during the patient's second hospital admission.

Meropenem, a sensitive drug, was used; however, as the antibiotic grade was high, it could have led to the creation of superbugs. The patient's second culture of *K. pneumoniae* was not sequenced to determine whether it was hvKP, which represents another limitation of the patient's treatment. Sequencing should be performed if a patient develops a recurrent *K. pneumoniae* infection. Further, the use of an optimal first-line antibiotic to treat *K. pneumoniae* infection should be considered to prevent a recurrence. It is unknown whether the initial use of meropenem to treat the infection during the patient's first hospitalization could have prevented the second hospitalization and miscarriage, and the optimal dose and duration of meropenem treatment to prevent the development of drug-resistant *K. pneumoniae* are unclear.

Our literature search identified only 1 similar case reported in recent years (18) of AC, PPROM, and early second-trimester miscarriage caused by *K. pneumoniae* infection during pregnancy. In that case, a 36-year-old mother was admitted at 18 weeks + 1 day of gestation with threatened abortion. The intrauterine fetal death (IUFD) occurred 11 days later. Posthumously, the fetus showed severe AC and fungal infection with neutrophils in the alveoli and the intestinal lumen filled with rod-shaped bacteria. Fetal blood and lung cultures were cultured for *K. pneumoniae*. The antibiotic profile showed piperacillin/tazobactam susceptibility. Three days after the IUFD, the mother developed a fever (of 37.8 ℃) for 1 week. Maternal blood and urine cultures were negative. Based on the fetal microbiology results, which were available 6 days after the IUFD, the initial treatment of amoxicillin/clavulanate was switched to piperacillin/tazobactam, and the patient recovered completely. Thus, in the event of PPROM and IUFD, fetal microbiological testing should always be performed to determine the causative pathogen and the appropriate antibiotic treatment. *K. pneumoniae* is an opportunistic pathogen.

In relation to the patient in the present case study, bacteremia led to a miscarriage, and the source of infection was unidentified. Liver abscesses, lung abscesses, or kidney abscesses are commonly observed with *K. pneumoniae* infections. However, there was no obvious clinical symptoms in this patient; only renal cysts were found at the time of discharge, and the results of the urinalysis and urine culture were negative, which did not conform to the pathogenesis of *K. pneumoniae*, and which was also specific to this patient. In addition, blood and lung cultures were not performed in the aborted fetus.

This patient has had a total of 3 miscarriages. After the first spontaneous abortion, she was found to have uterine septum and underwent surgery. The patient had a spontaneous abortion after PPROM at 16 weeks in 2019 and had a third spontaneous abortion. *Klebsiella* spp., and placental examinations suggest that this symptom in line with stage III chorioamnionitis, which may indicate that the abortion was caused by infection. Additionally, infection is a cause of recurrent abortion.

Reports from other countries suggest a significant correlation between female reproductive tract health-related infections and abortion. The most common pathogens are *E. coli* (31.5%), *Enterobacter* (18.4%), *K. pneumoniae* (12.5%), *Enterococcus faecalis* (11.6%), *Staphylococcus aureus* (10.2%), and *Pseudomonas aeruginosa* (8.4%). The study identified a

significant association between health care-related female reproductive tract infections and a history of miscarriage (18). However, no association was found between HAIs and a history of preterm births (19).

Recurrent miscarriage is a serious psychological and economic problem. The etiology of the vast majority of cases is unknown, or at best not understood. *K. pneumoniae* infections have been reported during pregnancy in humans and animals; however, there is little information on whether these infections contribute to early pregnancy loss (20). If a miscarriage is caused by infection, the patient must pay attention to the prevention of infection when the patient becomes pregnant again; for example, sensitive antibiotics should be used as soon as possible. This patient was 40 years old and thus had a high-risk pregnancy, and fetal chromosomal abnormalities cannot be ruled out. The lack of fetal chromosome testing is also a limitation of the patient's treatment. If PPROM results in a miscarriage, microbial cultures of fetal blood and tissue are necessary to find the causative agent, followed by antibiotic therapy.

Conclusions

The present case provides guidance on how to treat pregnancy complicated by *K. pneumoniae*, how to prevent miscarriage, and how to prevent the formation of drug-resistant bacteria and the production of super bacteria. In addition, unlike in other infections, the hemogram of this patient was only characterized by an increase in the absolute neutrophil count, while the total WBC count did not increase. Finally, further studies need to be conducted to gain an understanding of the virulence of *K. pneumoniae*, and the optimal duration of treatment needs to be determined.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1334/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1334/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Medical Ethics Committee of the Second Hospital of Shanxi Medical University (No. 2022YX088). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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