Intrapleural perfusion hyperthermia improves the efficiency of anti-PD1 antibody-based therapy for lung adenocarcinoma: A case report

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Abstract. Chemotherapy based on intrapleural perfusion hyperthermia (IPH) can markedly improve the sensitivity of lung adenocarcinoma cells to anti-programmed cell death receptor 1 (PD1) antibody adjuvant chemotherapy and enhance the clinical response of a patient. In the present study, a unique case of a patient who failed to respond to immunotherapy combined with chemotherapy but achieved prolonged stable disease after treatment with IPH and subsequent sintilimab-based treatment, is reported. A 50-year-old Chinese female patient was admitted to a regional cancer hospital presenting with hemoptysis and persistent fever. The findings of computed tomography imaging and thoracic puncture tissue biopsy indicated a diagnosis of adenocarcinoma. The TNM and clinical stage were identified as cT2N3M0 and stage IIIB, respectively. Immunohistochemical tests showed the expression of programmed death-ligand 1 (PD-L1) with a tumor proportion score of 2%. No other classic genetic alterations were detected. Initially, sintilimab-based chemotherapy at 200 mg was administered, for three cycles from April 2020, and increased pleural effusion was observed on the left side. The best overall response (BOR) assessment of the local lesion was progressive disease. IPH combined with chemotherapy was then carried out from August to September 2020, after which the same course of sintilimab-based chemotherapy as aforementioned was provided from October 2020 to September 2023. The BOR evaluation results during the monotherapy courses were all judged as stable disease. Therefore, it was concluded that IPH can substantially improve the efficiency of anti-PD1 antibody-based therapy for lung adenocarcinoma.

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Introduction

Immunotherapy has led to great progress in anticancer therapy (1). Immunotherapy activates the patient's own immune system to fight cancer (1,2). Therefore, compared with conventional chemotherapy or targeted therapies, reactivation of T cells by immunotherapy can more efficiently kill tumor cells and prevent cells from escaping the immune system, and is less prone to drug resistance (2).

Immune checkpoint inhibitors (ICIs) are currently used as an alternative treatment option for patients with advanced lung adenocarcinoma (3). Sintilimab, a recently developed human IgG4 monoclonal antibody, can bind to programmed cell death receptor 1 (PD-1) and block related pathways (4). It has been approved in China for the treatment of advanced lung adenocarcinoma (5). According to clinical trial data, sintilimab also exhibits considerable antitumor effects in non-small-cell lung cancer (NSCLC) (6). The expression of programmed death-ligand 1 (PD-L1), a PD-1 receptor and immune checkpoint mainly expressed on the surface of activated T cells, can be evaluated by immunohistochemistry and is the only prognostic marker approved for clinical use to evaluate the efficiency of anti-PD1 antibody-based lung cancer therapy (7). A low tumor proportion score (TPS) of PD-L1 always indicates that the response to PD-1 inhibitors will be deficient (8). Generally, a PD-L1 TPS >1% is regarded as the lower threshold for use of anti-PD1 antibody-based adjuvant therapy according to global guidelines such as the National Comprehensive Cancer Network (NCCN) or the European Society for Medical Oncology (ESMO) (9,10).

Malignant pleural effusion (MPE) is a common complication of advanced lung cancers (11). It occurs in 30% of lung cancer cases and indicates poor prognosis (12). MPE also contributes to immunosuppression in advanced lung cancers, although the detailed mechanism by which this

occurs remains obscure (13). Tumor-associated macrophages (TAMs), which are normally detected in the MPE, can impair the activation of T lymphocytes and natural killer cells and exert an immunosuppressive function (14). In addition, a series of immunosuppressive cytokines, such as IFN-γ, IL-4, IL-6, IL-1β and CXCL1, secreted by cancer cells suppress the host immune response and thereby promote tumor progression (15). $CD8^+$ T cells from MPE samples display insufficient differentiation and show a partial response to anti-PD-L1 therapy (16). Intrapleural perfusion hyperthermia (IPH) is a relatively new technique that involves intrapleural perfusion with a hyperthermic liquid combined with chemotherapeutic agents (17). IPH can efficiently exhaust the MPE and inhibit the malignant progression of cancers (17,18).

In the present case report, a clinical case with advanced lung adenocarcinoma who was refractory to sintilimab-based chemotherapy but benefited from IPH therapy, is reported. Subsequently, the patient continued to receive sintilimab and pemetrexed combination treatment and maintained a stable disease (SD) state for >36 months. This outcome highlights the potential of IPH as an alternative method to overcome deficient response to PD-I inhibitors and improve the overall survival of patients.

Case report

A 50-year-old woman was admitted to The Affiliated Hospital of Hebei University, Baoding, China) in March 2020. The clinical presentation of the patient was characterized by hemoptysis and persistent fever, and the patient complained of pain in the left scapular area. The patient did not have a history of smoking or drinking. In April 2020, the patient was diagnosed with lung adenocarcinoma with a small amount of MPE, following emission computed tomography (CT) whole-body bone imaging; enhanced CT of the chest, abdomen, and pelvic cavity and histopathological examination (hematoxylin-eosin staining) of tissues from a thoracic puncture tissue biopsy. Furthermore, the TNM and clinical stage were identified as cT2N3M0 and stage IIIB, respectively (Fig. 1A and B). Immunohistochemical assessment showed PD-L1 expression with 2% TPS (Fig. 2A and B). The biopsies were then subjected to genetic testing via the target region sequence of 520 cancer-related genes which contained 520 cancer-driven and sensitive genes (OncoScreen Plus panel; Burning Rock Medical Laboratory Co., Ltd.). The panel was designed according to the information of the OncoKB (Burning Rock Medical Laboratory Co., Ltd.) (19). The Genomic DNA was extracted by the Genomic DNA Isolation Kit (cat. no. K281-50; BioVision, Inc.). The DNA was then fragmented using ultrasound. Subsequently, the DNA was separated using 2% agarose gel electrophoresis. The fragment (range from 200 to 500 bp) was harvested by QIAquick Gel Extraction Kit (cat. no. 28704; Qiagen, Inc.). The DNA integrity and concentration number was determined using the Lab-on-a-Chip-System Bio-analyzer 2100 (Agilent Technologies, Inc.). The targeted DNA region was captured by the specific probe sets (the probe sets were designed by Burning Rock Medical Laboratory Co., Ltd. and synthetized by Agilent Technologies, Inc.). PCR was used to amplify the captured DNA region. The paired-end adaptors with nucleotide barcodes were linked to the enriched DNA to prepare the sequencing library using the NEB Next Ultra II DNA Library Prep Kit (cat. no. E7645L; New England BioLabs, Inc.). The average insert fragment was 299 bp which was measured using Bio-analyzer 2100. The final concentration of the library was determined using Qubit 2.0 Fluorometer (Thermo Fisher Scientific, Inc.). The loading concentration of the library was then adjusted to 10 ng/μl. The library was then sequenced using HiSeq X Ten (Illumina, Inc.). The paired-end 150-bp (PE150) sequencing model was converted using bcl2fastq Conversion software (v2.20.0.422), to convert raw sequencing data to fastq format (Illumina, Inc.). The FastQC (v0.10.0, (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) software was used to control the data quality. The SNP calling was performed using MuTect (v1.1.4; broadinstitute.org/cancer/cga/mutect) software. The relationship between the mutations and chemotherapy drug susceptibility referred to the NCCN Guidelines (https://www.nccn.org/) and OncoKB. The results were summarized as follows: the *KRAS* gene mutation abundance was 38.2%; the *CDK2A* gene was partially deleted; and the *MYC* and *RICTO* genes were amplified. Immunotherapy combined with chemotherapy was considered. Initially, the patient received four courses of palliative chemotherapy from April to June 2020. The regimen for each course consisted of 200 mg sintilimab every 3 weeks, with 800 mg/m^2 pemetrexed on day 1 and 50 mg lobaplatin on day 2. Subsequently, enhanced CT examination of the chest showed increased pleural effusion and left upper lobe atelectasis in the left thoracic cavity. The main symptoms were a choking sensation in the chest, expiratory dyspnea, and a persistent fever. The best overall response (BOR) assessment of the local lesion was SD. Pleural puncture for hydrops outflow was then carried out. Hydrothorax cells were harvested by centrifugation(1200 g, 4˚C, 5 min). Immunohistochemical staining of biomarkers of the embedding cells indicated $CK5^-$, $NapsinA^+$, $P40^-$, $CK7^+$ and $TTF\text{-}1^+$ (Fig. 3A-E). Furthermore, pathological examination of cell proportions indicated that large number of lymphocytes and severely dyskaryotic cells were present in the hydrothorax.

After a multidisciplinary discussion, the patient received four courses of IPH followed by chemotherapy with cisplatin (a total of 60 mg, circulation 20 mg and retained 600 mg) from August to September 2020. Following the treatment, the hydrothorax was found to have been effectively controlled. Then, six courses of immunotherapy and chemotherapy were performed from September to October 2020. The regimen for each course was as follows: 200 mg sintilimab was administered at day 0, 800 mg/m^2 pemetrexed at day 1, and lobaplatin 50 mg at day 2. Lung CT was performed after the adjuvant chemotherapy and indicated that the stigmatal tubercle had shrunk, the left upper lobe atelectasis was released, and hydrothorax content was significantly reduced (Fig. 4A-C). No other symptoms were observed after this therapy.

Given that the IPH-adjuvant chemotherapy obviously weakened the patient, 26 courses of immunotherapy-adjuvant monotherapy were subsequently performed from October 2020 to September 2023. The regimen for each course was as follows: 200 mg sintilimab was administered at day 0, and 800 mg/m^2 pemetrexed at day 1. Lobaplatin was excluded from the regimen. Following courses 6, 8, 11, 14, 17, 20 and 26, a BOR assessment was performed based on enhanced CT of the

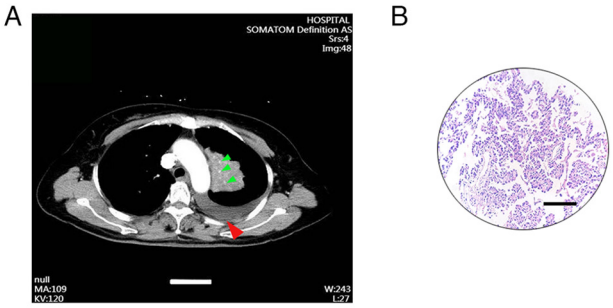

Figure 1. Chest computed tomography and histopathological examination of the patient at first visit. (A) Image captured on April 10, 2020. Red arrows indicate intrapleural perfusion hyperthermia; green arrows indicate diffuse pulmonary nodules in the left lobe. (B) Hematoxylin and eosin staining of tumor tissues from thoracic puncture tissue biopsy. Scale bar, 100 μm.

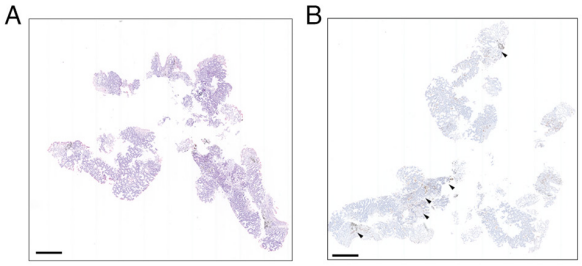

Figure 2. H&E and IHC staining of lung adenocarcinoma from thoracic puncture tissue biopsy. (A) H&E staining. (B) IHC staining of PD-L1. The arrowhead indicates positive cells. Scale bar, 100 μm. H&E, hematoxylin and eosin; IHC, immunohistochemical.

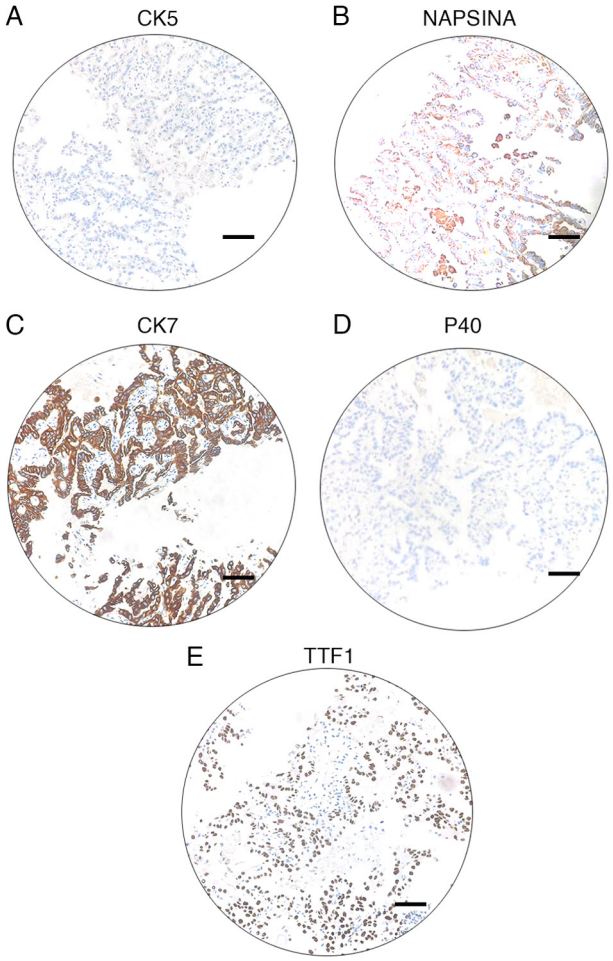

Figure 3. Immunohistochemistry staining of (A) CK5, (B) NapsinA, (C) CK7, (D) P40 and (E) TTF-1 in embedded cells harvested from the pleural effusion. Scale bar, 100 μm.

thoracic and abdominal tumors. Data obtained from evaluation of the CT images at different treatment stages are summarized in Table I. The BOR evaluation results were all SD, indicating that the malignant progression of the tumor was under control. To date, the patient remains alive, with a BOR stage of SD.

Discussion

ICI-based adjuvant chemotherapy has been previously developed and adopted for treatment of advanced lung cancer. PD-1 inhibitor sintilimab, which has pharmacokinetic properties similar to those of nivolumab, has been approved by the Chinese National Medical Products Administration and the US Food and Drug Administration to treat NSCLC (4). Owing to its safety and pharmacoeconomic advantages, it has widely been adopted for clinical practice in China. However, there are numerous issues that can result in drug resistance and failure of ICI treatment (20). The tumor microenvironment (TME) that surrounds the tumor cells contains various types of immune cells, including macrophages, natural killer cells, myeloid-derived suppressor cells, and T lymphocytes (21). The activation of T lymphocytes in the TME affects the efficiency of ICI-based chemotherapy; continuous antigenic stimulation of T cells has been linked to increased expression of PD-1, which leads to T-cell exhaustion (22). Increased expression of the PD-1/PD-L1 axis in tumor cells is associated with poorer prognosis (20). ICIs can block the binding between PD-1 and PD-L1/L2 and restore the endogenous antitumor T-cell response (20,22).

MPE occurs in 30% of lung cancers and is regarded as signature for poor prognosis that promotes the malignant progression of the cancer (20). The immune impairment caused by immune suppressors in the MPE has been reported previously. A number of cytokines and chemokines in the MPE can serve as prognostic markers (23). For example, $CD163^+$ TAMs were identified as potential diagnostic and prognostic biomarkers for MPE that could be used to evaluate the effects of therapy (23,24). Furthermore, TAM-derived TGF-β can lead to dysfunction of $CD4^+$ and $CD81^+$ cells and impair T-cell cytotoxicity in the MPE. Generally, PD-L1-expressing tumor cells in the MPE are considered to inhibit the cytotoxic potential of $CD8^+$ T cells (25). Therefore, ICIs can block PD-L1 and reduce the volume of the MPE. However, the mechanism underlying ICI resistance in the MPE remains unclear. In the present case report, a patient who experienced ICI treatment failure and increased volume of MPE, was reported. The findings indicate that the clinical, immunological, and pathological indices in the MPE may provide insight into the potential mechanism by which MPE contributes to ICI resistance.

The treatment of advanced lung cancer with MPE is a major challenge for thoracic surgeons (26), and no superior clinical strategy has yet been identified. Pleurodesis and pleurectomy are commonly used surgical methods (18,26); however, the

Table I. Image evaluation of the CT imaging.

CT scan findings	First visit	Following the first phase of sintilimab treatment	Following IPH treatment	Following the fourth phase of sintilimab-based treatment after IPH treatment
Relative representative area of MPE (%)	13%	45%	Not detected	Not detected
Location of the MPE	Left	Left	N/A	N/A
Number of diffuse pulmonary nodules	4	13	8	8
Estimated tumor diameter (cm)	1-2	2-3	2-3	2-3
Mediastinal pleural thickening	Observed	Observed	Observed	Observed
Circumferential pleural thickening	Observed	Observed	Observed	Observed

CT, computed tomography; IPH, intrapleural perfusion hyperthermia; MPE, malignant pleural effusion.

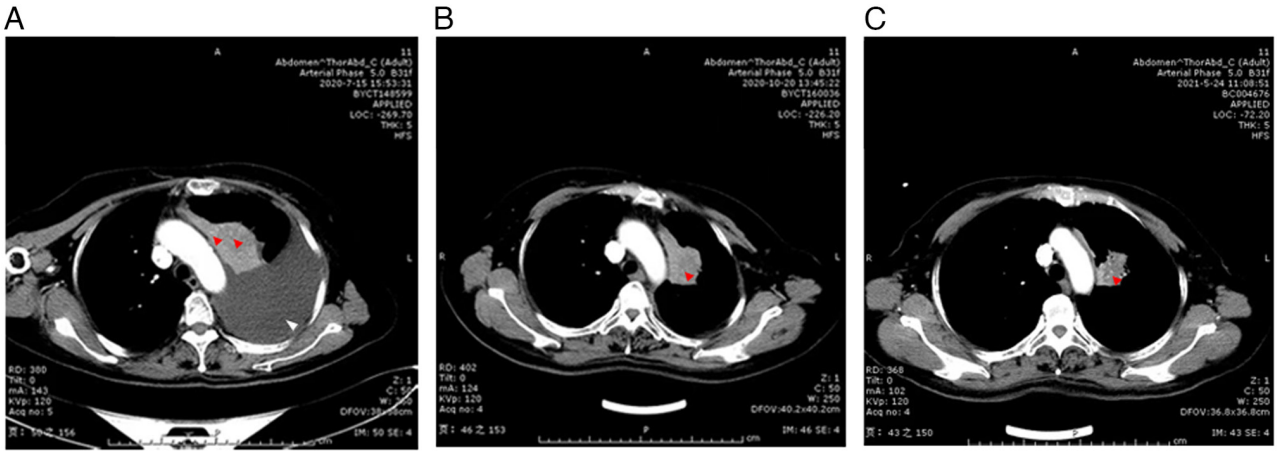

Figure 4. Enhanced chest computed tomography of the patient to assess disease status and progression before and after treatment with intrapleural perfusion hyperthermia-adjuvant chemotherapy. (A) Image captured on August 23, 2020. Red arrows indicate metastatic focus before treatment. High-density arc-shaped shadows indicate the malignant pleural effusion (white arrows). (B and C) Images captured on September 23, 2020 and April 10, 2021, respectively. Red arrows indicate metastatic focus, showing that the tumor size has decreased after treatment and following chemotherapy.

condition of the patient may limit the feasibility and efficiency of this operation. A retrospective study explored the reasons for the poor prognosis of patients with disseminated pleural cancer with MPE when treated by lung resection. Kodama *et al* (27) first observed favorable clinical outcomes of the patients with MPE who received IPH combined with chemotherapy, and a case with a mean survival time of 20 months after lung resection and IPH was reported in another study (28). In the present study, IPH combined with chemotherapy similarly extended the survival of the patient to 30 months following lobaplatin and pemetrexed combined therapy. In recent decades, IPH-based therapies have become a standard strategy for treatment of MPE (29,30), although in most reports, IPH therapy is combined with chemotherapy or surgery (30-32). The efficiency and safety of these methods depend strongly on the physical condition of the patient and the resectability of tumors (29,31,33). There have been few reports of the relationship between IPH and immunotherapy. The patient in the present case report also had a low PD-L1 positive ratio (accounting for ~2%), which is regarded as a prognostic factor indicating poor response to ICI treatment. However, the histopathology, genetic mutations, and clinical features of this tumor did not suggest a poor prognosis. Increased MPE was observed after phase 1 treatment and may be a possible explanation for the poor efficacy of the sintilimab-based chemotherapy. Following IPH treatment for nearly 1 month, MPE was no longer generated during the subsequent sintilimab-based chemotherapy. This clinical presentation indicates that IPH-based chemotherapy may improve the sensitivity of cancer cells to the ICIs. It also supports a previous finding that demonstrated that IPH could convert the phase of T cells from Th1 to Th2 in patients with lung cancer (34). Therefore, effective and safe activation of the immune system in response to ICIs may be the key to treatment.

Several local treatment methods are used as standard treatments for unresectable tumors (35). There is a consensus among some specialists that appropriate radiation therapy (RT) can enhance the efficacy of ICIs, with manageable toxicity, in patients with lung cancer (36). The efficiency of RT largely depends on the clinical stage and on personalized tumor histology and molecular status. In addition, different radiation doses in a single-fraction or short-course fraction regimen, such as hypofractionated radiation, particle implantation, and radiofrequency ablation, may induce diverse immunogenic effects. In a hypofractionated radiation model, researchers demonstrated that 3x8 Gy was the most effective scheme compared with other fractionation protocols (18x2 or 1x16.4 Gy) when combined with anti-PD-L1 therapy (37).

Therefore, a series of hypofractionated radiation therapies such as particle implantation and radiofrequency ablation have been developed for ICI combination treatment. The implantation of radioactive particles has been demonstrated to be highly efficient in the treatment of middle- to late-stage lung cancer. For instance, ^{125}I combined with chemotherapy is widely used for lung cancer therapy (38). To date, most reports of radiofrequency ablation treatment for cancer have involved colorectal cancer, and it has shown significant clinical value in the treatment of colorectal cancer and liver metastasis (39). Palussière *et al* (40) demonstrated that the combination of ICIs with percutaneous thermal ablation is an important therapeutic option for NSCLC treatment. However, the safety and efficiency of such methods still needs to be explored. The development of efficient and low-toxicity delivery methods is another aspect to be considered with respect to hypofractionated radiation. In recent decades, the development of nanomedicine has resulted in new methods and perspectives for local treatment. Nanoparticles have been widely used in medical imaging, photothermal therapy and photodynamical therapy (41). Owing to their excellent properties (including good biocompatibility and biodegradation, low toxicity and high specificity), bionanoparticles have emerged as a new type of anticancer adjuvant in recent years (41). For instance, a dendrimer formed from several nanoparticles was shown to activate specific immune cells and facilitate cancer immunotherapy (42). A nanoparticle-based laser desorption/ionization mass spectrometry platform also greatly improved the specificity of metabolic fingerprinting in lung adenocarcinoma; when integrated in a deep-learning model with other classical cancer hallmarks, it could efficiently detect lung adenocarcinoma at an early stage (43). These findings indicate that combining the appropriate nanoparticles with a radioactive element may greatly improve the specificity and sensitivity of RT and may lead to the development of an optimal delivery carrier for RT treatment in future.

In summary, combination of a dosage-controlled RT agent with IPH may be a more efficient means of achieving a favorable therapeutic outcome than IPH combined with chemotherapy. This finding has special significance for patients for whom chemotherapy or surgical treatment is not suitable and may indicate an alternative direction for the development of IPH-based treatment in future. A limitation of the present case report is that only a single patient was reported. Therefore, studies with more subjects or prospective/retrospective cohort studies are required to verify the findings of the present study in the future. In addition, mechanistic research, clinical trials and real-world studies are also warranted to investigate the feasibility of combining various ICIs, RT-based local treatment, nanomedicine and IPH for patients with various pathologies, genetic mutations and clinical features.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the SRA repository, (https://www.ncbi.nlm.nih.gov/sra/PRJNA1063833).

Authors' contributions

XW, JS, LH, GR, NG and ZS made substantial contributions to the conception and design, acquisition of data, as well as analysis and interpretation of data. XW and JS made substantial contributions to develop the treatment protocol, acquisition of data and analysis, and wrote the manuscript. LH carried out the collection of samples and managed the information received from the patient and performed the follow-up. GR participated in the data analysis. GR and NG contributed to the experimental design and the literature review. ZS revised the manuscript. XW and ZS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study conformed to the ethical standards for human subjects involved in medical research. The Ethics Committee of the Affiliated Hospital of Hebei University (Baoding, China) approved (approval no. 20220923) the present study. The research was carried out in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for participating in the present study.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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