CASE REPORT
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PRaG Therapy for Advanced Penile Squamous Cell Carcinoma with Abscopal Effects: A Case Report

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Abstract: Advanced metastatic penile squamous cell carcinoma (PSCC) is a rare and highly aggressive malignancy, for which current guidelines have not reached a consensus on second-line treatment, making clinical management extremely challenging. The effectiveness of immune checkpoint therapy for metastatic PSCC is very limited. Exploring new approaches to enhance the efficacy of immunotherapy is crucial, and the triple therapy of stereotactic body radiotherapy (SBRT) combined with Programmed Cell Death Protein 1 Inhibitor (PD-1 inhibitor) and granulocyte-macrophage colony-stimulating factor (GM-CSF), abbreviated as PRaG, may be a promising treatment strategy. The case report examines the efficacy of PRaG therapy (SBRT combined with PD - 1 inhibitor and GM-CSF) in advanced metastatic penile squamous cell carcinoma (PSCC), a rare and aggressive malignancy with no consensus on second-line treatment. A 65-year-old male, diagnosed with PSCC in December 2020 and having multiple metastases after recurrence in May 2021, showed disease progression again in December 2021 following first-line chemotherapy. Administered PRaG therapy due to lack of standard subsequent treatments per NCCN guidelines, the patient exhibited remarkable sensitivity with targeted radiation and abscopal effects. The patient underwent three sessions of PRaG therapy, achieving favorable therapeutic outcomes and mild side effects. PRaG therapy may provide an alternative for the treatment of patients with advanced recurrent or refractory cancer.

Keywords: PRaG therapy; Penile squamous cell carcinoma; PD-1 inhibitor; SBRT; GM-CSF.

Introduction

Penile cancer is a relatively rare malignancy, predominantly affecting male patients aged 50 to 70. According to GLOBOCAN 2020 data, there were 36,068 new cases of penile cancer globally in 2020, with 13,211 deaths, ranking 30th in incidence and 31st in mortality among the most common cancers recorded worldwide[1]. The most common pathological type of penile cancer is squamous cell carcinoma, accounting for over 95% of cases. Penile squamous cell carcinoma (PSCC) is an aggressive disease, with approximately 40% of newly diagnosed patients presenting with lymph node metastasis, and the five-year survival rate for patients with advanced metastasis is only 9%[2].

Due to the rarity of PSCC, most randomized clinical trials evaluating the efficacy of immune checkpoint inhibitors (ICI) in the treatment of PSCC are phase II or III trials, and the subjects enrolled in these trials are often those with rare malignancies, MSI-H, and HPV-positive tumors[3]. According to the 2023 edition of the NCCN Guidelines, TIP (cisplatin, ifosfamide, and paclitaxel regimen) is the recommended first-line treatment option for patients with metastatic penile cancer, and the combination of 5-FU and cisplatin can be used as an alternative to TIP[4,5]. Although some patients may benefit from this regimen, due to its toxicity, some patients in the real world require dose reduction[5,6]. The guidelines do not recommend a standard treatment regimen for second-line therapy, but for patients with high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) tumors, or Tumor Mutation Burden (TMB) ≥ 10 mut/Mb, pembrolizumab may be considered[7,8]. Given the very limited role of immunotherapy in advanced metastatic PSCC[9,10], exploring new sensitization strategies for immunotherapy is crucial.

In recent years, we have aimed to improve the response rate to anti-PD-L/PD-L1 therapy by combining immune checkpoint inhibitors with radiotherapy, chemotherapy, anti-angiogenic therapy, or other immunomodulatory drugs. Among these approaches, the combined use of PD-1 inhibitors, radiotherapy, and GM-CSF for the treatment of advanced refractory tumors is considered as an innovative cancer treatment strategy. This approach was first proposed by Professor Zhang Liyuan from the Second Affiliated Hospital of Soochow University in 2019 for the treatment of patients with metastatic solid tumors refractory to chemotherapy. PRaG Therapy is essentially in line with the theory of the cancer immunity cycle, where radiotherapy causes tumor antigen exposure, GM-CSF promotes the activation and proliferation of antigen-presenting cells, and PD-1 inhibitors activate specific CD8 + T lymphocytes to kill tumor cells, working synergistically to form an effective tumor immune response[11].

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Here, we introduce a case of a patient with advanced PSCC with high PD-L1 expression who achieved significant remission and abscopal effects after treatment with triple therapy of PD-1 inhibitor combined with large-fraction radiotherapy and granulocyte-macrophage colony stimulating factor (GM-CSF).

Case presentation

The schematic diagram of the patient's entire treatment is shown in Fig. 1. In December 1, 2020, a 65-year-old male patient was diagnosed with PSCC and underwent partial penectomy and bilateral inguinal lymph node dissection at a hospital in Dalian. The patient had no special personal history, no familial genetic disease. Postoperative pathology indicated moderately differentiated squamous cell carcinoma of the penis, with cancer tissue invading the corpus spongiosum and cancer emboli seen in blood vessels (see in supplement Fig. 1). Cancer metastasis was observed in the left inguinal lymph node (1/2). According to postoperative pathology, the patient was staged as either pT2 or pT3 (pT2-3) N1M0. Unfortunately, no adjuvant therapy was administered after surgery. In May 2021, the patient visited our department due to enlargement of the left inguinal lymph node. Physical examination revealed a palpable, enlarged lymph node in the left inguinal region, with a diameter of approximately 2.5 cm, hard in consistency, fixed, and with mild tenderness. Chest and abdominal CT scans revealed multiple metastatic lesions in both lungs, a nodule at the left margin of the pericardium, and enlarged left inguinal lymph nodes. Subsequently, a coarse needle biopsy of the patient's inguinal lymph node confirmed the metastasis of penile cancer, and immunohistochemistry indicated a PD-L1 TPS score of 61% and a CPS score of 73. According to the NCCN guidelines, the patient received two cycles of TP regimen (paclitaxel 210 mg + cisplatin 30 mg d1-4) treatment from May to June in 2021, and the efficacy was evaluated as a major partial response (PR) after two cycles. The patient experienced multiple adverse reactions after chemotherapy, including grade III bone marrow suppression, gastrointestinal adverse reactions, and fatigue. In July 2021, the patient underwent one round of reduced-dose chemotherapy (paclitaxel 180 mg + cisplatin 30 mg d1-3), but it was terminated due to intolerable adverse reactions.

Unfortunately, in December 2021, the patient returned to the clinic with a chief complaint of enlarged left inguinal lymph nodes. CT scans revealed multiple metastatic lesions in both lungs, enlarged left inguinal lymph nodes, and a nodule at the left margin of the pericardium, which were significantly larger compared to previous CT scans (July 2021). The tumor was assessed as progressing again. Considering that the guidelines do not recommend a second-line standard treatment for metastatic or recurrent penile cancer, and the patient was unable to tolerate chemotherapy, while no suitable clinical trial was found, the patient chose to try the PRaG treatment for advanced tumors. Due to financial reasons, the patient opted for the cheapest domestically produced PD-1 inhibitor, Sintilimab. We fully informed the patient of the purpose of the treatment and the potential risks, and he signed the informed consent form and the self-funded medication notification form.

The patient received the PRaG Triplet Therapy since December in 2021. The patient started the PRaG 1.0 therapy on December 11, 2021, with the specific treatment plan for the first cycle as follows: After completing radiotherapy (18 Gy/3f, d1-3) for the metastatic lesion in the right upper lung, the patient received topical GM-CSF (200 μg, once daily, subcutaneous injection from d4-17), and on the eighth day, the PD-1 inhibitor (Sintilimab 200 mg, d8) was administered. In January 2022, a follow-up CT scan revealed a significant reduction in the radiotherapy target lesion (metastatic lesion in the right upper lung), as well as marked shrinkage in other lung metastases and inguinal lymph nodes, demonstrating the rare abscopal effect induced by PRaG therapy (see in Fig. 2).

Subsequently, the patient underwent the second cycle of PRaG therapy. For the second cycle, we selected the lesion located at the lateral margin of the left lower lung as the radiotherapy target, with sequential administration of GM-CSF and PD-1 inhibitor therapy. To our delight, the patient experienced abscopal effects again, with regression observed in both the target and non-target lesions (see in Fig. 3). Since the lung lesions had shrunk significantly after two cycles of PRaG therapy, we were unable to find suitable lung targets for the third cycle. Instead, we had to choose the enlarged left inguinal lymph node. To prevent edema caused by impaired lymphatic return in the left lower limb, we employed a combination of electron beam and X-ray irradiation (electron beam, 8Gy/2f + X-ray 10Gy/2f). After radiotherapy, the patient's inguinal lymph nodes basically regressed completely, and the local skin showed pigmentation caused by radiotherapy (see in Fig. 4). Following this, the patient continued with maintenance therapy using the PD-1 inhibitor Sintilimab monotherapy, administered once every three weeks. Throughout the three cycles of PRaG therapy and maintenance treatment, the patient did not experience any adverse events such as immune-related pneumonitis, thyroid dysfunction, myocarditis, or others. However, in September 2022, the patient's family informed us that the patient had passed away due to severe lung infection complicated by COVID-19.

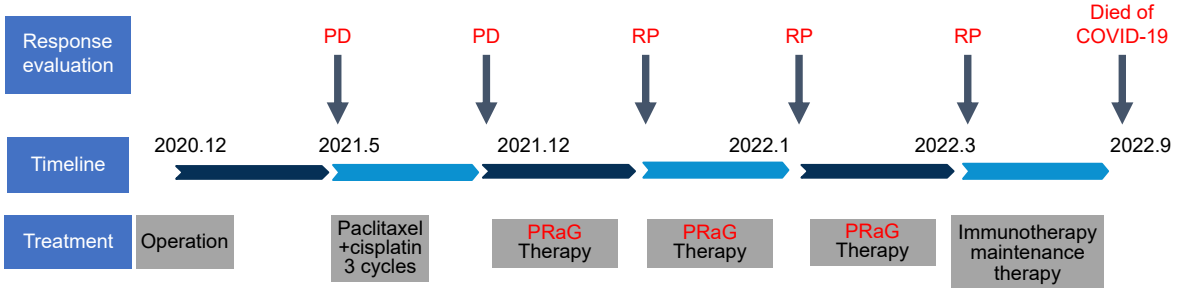


Fig. 1. Timeline of different treatments and disease status.

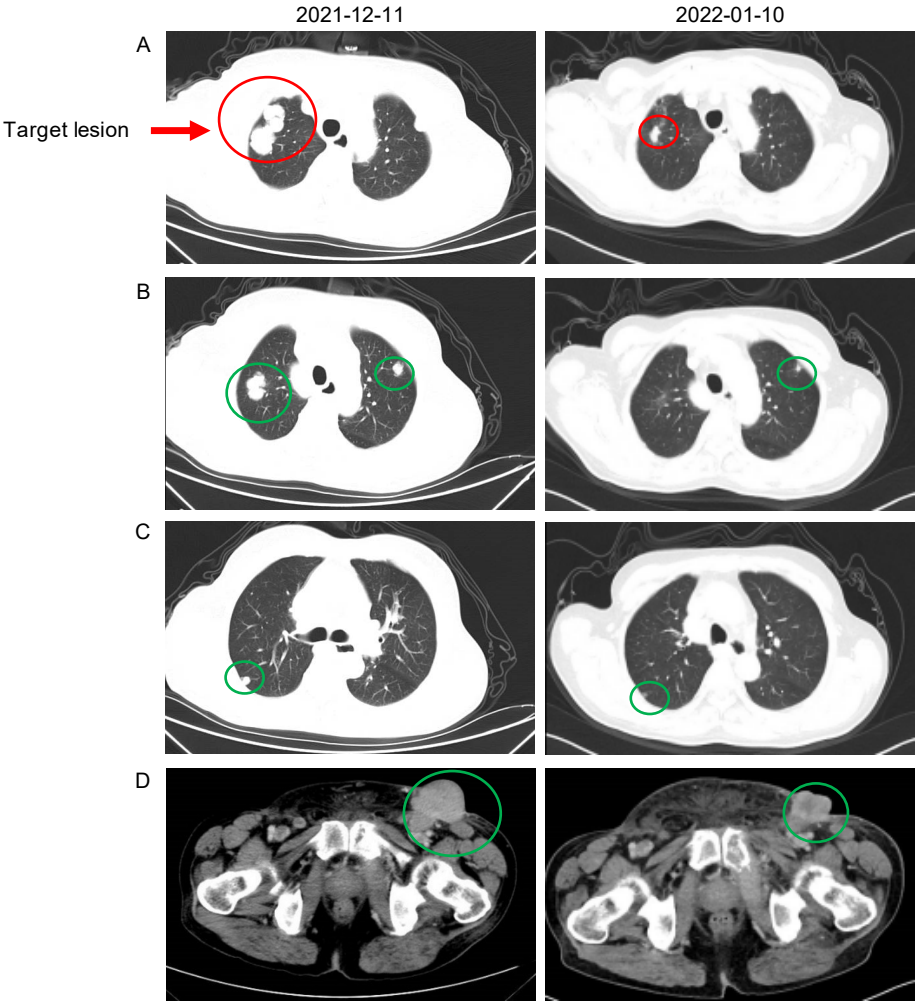
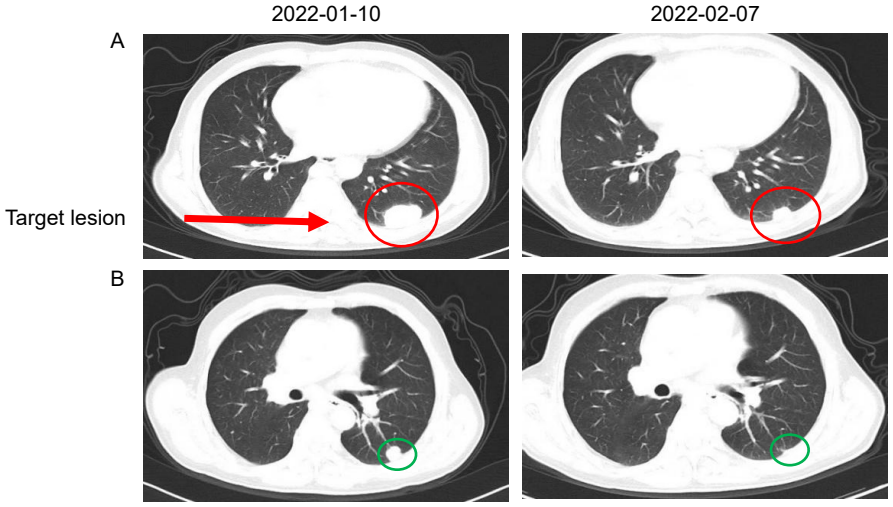


Fig. 2. CT scans were conducted before (2021-12-11) and after (2022-01-10) the first cycle of PRaG 1.0 therapy.
A. Target lesions showed significant reduction.
B. The non-target lesions in both lungs showed significant reduction and even disappeared.
C. The right lower lobe pulmonary metastasis showed significant reduction.
D. The inguinal metastasis showed significant reduction.
The red area indicates target lesion, and the green earea indicates non-target lesions.



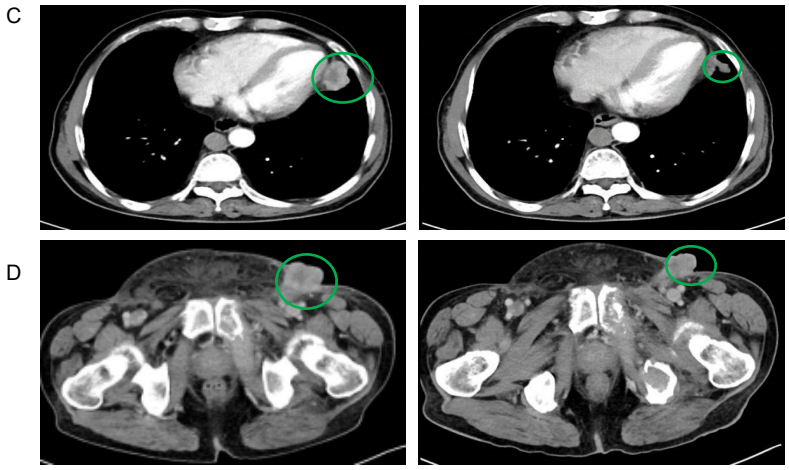


Fig. 3. CT scans were conducted before (2022-01-10) and after (2022-02-07) the second cycle of PRaG 1.0 therapy.
A. Target lesions showed significant reduction.
B. The left pulmonary metastasis showed significant reduction.
C. The metastasis at the left border of the pericardium showed significant reduction.
D. The inguinal metastasis showed significant reduction.
The red area indicates target lesion, and the green earea indicates non-target lesions.

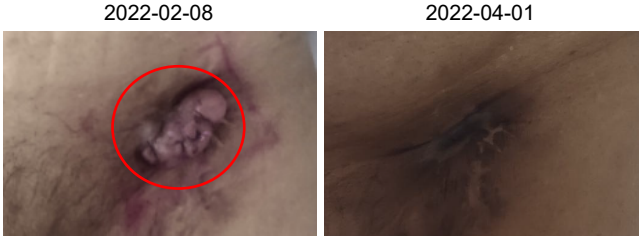


Fig. 4. Changes of inguinal lymph nodes before (2022-02-08) and after (2022-04-01) the third cycle of PRaG 1.0 therapy.
The red area indicates target lesion.

Discussion

The invasive late-stage metastatic or recurrent PSCC has a poor prognosis, and there is currently no standard second-line systemic treatment regimen recommended, making treatment very difficult[12]. This patient was a PD-L1 highly expressed recurrent metastatic penile cancer patient who experienced disease progression after surgery with a large tumor burden. After receiving three cycles of paclitaxel combined with cisplatin, the patient's condition was temporarily alleviated. However, due to the side effects of chemotherapy, the patient discontinued treatment, and the disease progressed rapidly afterward. The patient was unable to tolerate chemotherapy drugs but had a strong desire for treatment, so he chose to try the PRaG therapy, which combines hypofractionated radiotherapy with PD-1 inhibitors and GM-CSF.

The PRaG 1.0 study results demonstrated that when used primarily as third-line therapy, the objective response rate (ORR) to PRaG treatment reached 16.7% in tumor patients, with 5.6% of patients achieving complete response (CR)[13]. Following publication of the PRaG 1.0 study, multiple hospitals in China began employing PRaG therapy for salvage treatment of advanced refractory tumors. According to published literature, the treatment model has been successfully implemented in several domestic hospitals, with its application extending to various malignancies including refractory uterine leiomyosarcoma, gastric cancer, ovarian cancer, malignant perivascular epithelioid cell tumor, and thyroid cancer[14–18].

In recent years, cancer immunotherapy using immune checkpoint inhibitors has made significant progress in cancer treatment, especially PD-1 and PD-L1 inhibitors, which have changed the treatment paradigm of various cancers. PD-1/PD-L1 immune checkpoint inhibitors reactivate the immune response of T cells to tumor cells by blocking the interaction between PD-1 and PD-L1, fully utilizing the body's own immune system to resist the invasion of tumor cells. The expression of PD-L1 in tumor cells and tumor-infiltrating immune cells has been identified as a prognostic and predictive marker for various tumors[19–22]. PD-L1, MSI, and TMB are currently the three biomarkers approved by the FDA to predict the efficacy of immunotherapy[23]. A study analyzed 165 penile squamous cell carcinoma (PSCC) samples and found that high tumor mutation burden (TMB) is linked to strong PD-L1 expression, HPV negativity, and shorter overall survival, while low CTLA4 + cell infiltration indicates a poor prognosis. Notably, PD-L1 expression was found to have no significant impact on prognosis[24]. Another study examined 60 well-defined penile invasive carcinoma samples and found that immune cell infiltrate and tumor stage (pT) are significant prognostic markers for patient survival. Despite PD-L1 expression being detected in most samples, it was not significantly associated with overall survival[25]. A further study analyzed 213 patients with penile squamous cell carcinoma and found that diffuse PD-L1 expression and CD163 + macrophage infiltration in the tumor microenvironment are associated with lymph node metastasis. HPV negativity and diffuse PD-L1 expression are linked to poorer disease-specific survival[26].

Many studies have shown that the positive expression rate of PD-L1 in penile cancer tumor cells and tumor-infiltrating lymphocytes is relatively high in both epidemic and non-epidemic regions[25–27], suggesting that the PD-1/PD-L1 pathway may be a potential therapeutic target for such patients. A meta-analysis reviewed nine studies (involving 1,003 patients) to explore the relationship between PD-L1 expression and survival in penile cancer

patients. The results showed that the positivity rate of PD-L1 was 51.4%, and its high expression was associated with shorter cancer-specific survival, but not overall survival. PD-L1 was also related to tumor stage, grade, lymph node status, and HPV status. These findings suggest that overexpression of PD-L1 is associated with poor prognosis in penile cancer and can serve as a reference for selecting treatment strategies[28]. This patient had a highly immunogenic tumor with high PD-L1 expression, which may be one of the main reasons for its sensitivity to PRaG therapy.

During radiotherapy-induced tumor cell death, tumor antigens are released, along with various cytokines and chemokines, which upregulate immunogenic cell surface complexes such as PD-L1 expression and induce proinflammatory signals. This triggers the innate immune system to activate tumor-specific T cells, inducing a systemic anti-tumor immune response against both local and distant tumors[29–32]. Compared with traditional radiotherapy methods, high-dose ablative radiotherapy with fractionated dosing can enhance the anti-tumor immune response[33]. In this case, the patient received a total of three PRaG treatments. The first two treatments targeted larger metastatic lesions located on the outer edge of the lungs, using a large fractionated radiotherapy regimen of 6Gy*3f. Although the total dose was far lower than the conventional radical irradiation dose, fortunately, the patient achieved a significant partial response (PR), with a bystander effect and good tolerance. We chose lesions close to the outer edge mainly to reduce the radiation dose to surrounding normal lung tissue, thereby minimizing the occurrence of radiation pneumonitis. In fact, the patient did not experience any significant immune-related adverse events.

GM-CSF in PRaG treatment serves as a "catalyst" for tumor immunotherapy, promoting the proliferation and activity of macrophages and lymphocytes, continuously promoting the immune response. GM-CSF promotes the transformation of monocytes into M1 macrophages, improves immune suppression, and is also a crucial cytokine for the proliferation and differentiation of dendritic cells, thereby enhancing the immune system in tumor patients[34–36]. As a vaccine adjuvant, GM-CSF promotes the proliferation of antigen-presenting cells, which can enhance the incidence of the abscopal effect. A study published in The Lancet Oncology in 2015 indicated that GM-CSF can increase the incidence of the abscopal effect to 26.8% (11 cases), with the median overall survival (mOS) of patients experiencing the abscopal effect being extended by nearly 12 months and the risk of death reduced by two-fold[37]. The immune effects induced by GM-CSF and its role in promoting the occurrence of the abscopal effect are perfectly demonstrated in this case of advanced recurrent metastatic penile squamous cell carcinoma. After the first and second PRaG treatments, the patient experienced substantial regression in both target and non-target lesions, with promising therapeutic outcomes.

Unfortunately, the most regrettable aspect of this study is that the patient died unexpectedly from COVID-19, preventing us from observing his true progression-free survival (PFS) and overall survival (OS). However, given the patient's high sensitivity to PRaG treatment and the repeated occurrence of the abscopal effect, we have reason to believe that this is a highly successful case of PRaG treatment applied to advanced penile squamous cell carcinoma, which may be related to the patient's high PD-L1 expression.

Conclusion

In conclusion, advanced metastatic or recurrent PSCC is highly aggressive, lacks a standard second-line treatment regimen, has limited therapeutic options, and has a poor prognosis. In this case, the patient received a triple therapy of high-dose radiotherapy, GM-CSF, and PD-1 inhibitor immunotherapy, achieving multiple PR outcomes and repeated abscopal effects with excellent therapeutic efficacy. Additionally, the patient experienced mild adverse reactions. This salvage therapy regimen may provide a new treatment option for similar advanced tumor patients.

Abbreviations

CR, complete response; dMMR, mismatch repair deficiency; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICI, immune checkpoint inhibitors; mOS, the median overall survival; MSI-H, high microsatellite instability; ORR, objective response rate; PD-1 inhibitor, Programmed Cell Death Protein 1 Inhibitor; PFS, progression-free survival; PSCC, penile squamous cell carcinoma; SBRT, stereotactic body radiotherapy; TMB, Tumor Mutation Burden.

Ethics approval and consent to participate

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Authors' contributions

HM was responsible for study conception, clinical data collection and analysis, and drafting the manuscript. HXY and FG participated in clinical case management, assisted in data collection, and provided professional advice. All authors contributed to the study design discussion, reviewed and revised the manuscript, and approved the final version for publication.

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