



Leptomeningeal metastasis from *de novo* metastatic nasopharyngeal carcinoma: a case report

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Background: Leptomeningeal metastasis (LM) have a poor prognosis and rare studies have reported LM from nasopharyngeal carcinoma (NPC). Immune checkpoint inhibitor (ICI) was the standard first line treatment for metastatic NPC and was reported to improve intracranial response and survival in several types of cancer.

Case Description: In this case presentation, we present a case of a 26-year-old man with *de novo* metastatic NPC who initially complained of left cervical masses. A PET/CT and MRI scan revealed multiple liver, bone and brain metastasis. The patient received initial anti PD-1 antibody camrelizumab combined with chemotherapy, followed by radiotherapy to local and regional lesions. Two weeks after that, the patient experienced transient unconsciousness, persistent fatigue and pain in both lower limbs. Then MRI revealed leptomeningeal linear enhancement, hydrocephalus and increased multiple intracranial metastatic lesions. So the patient was diagnosed of LM. The therapeutic regimen then consisted of whole brain radiotherapy combined with oral capecitabine. A partial response was demonstrated and the progression-free survival (PFS) was 5 months since the diagnosis of LM. To our knowledge, this is the first case of LM from NPC treatment with ICI.

Conclusions: This case highlights the diagnosis and treatment of LM from NPC, and provides an optional regimen after ICI failure.

Keywords: Leptomeningeal metastasis (LM); nasopharyngeal carcinoma (NPC); immune checkpoint inhibitor (ICI); chemotherapy; case report

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Introduction

Nasopharyngeal carcinoma (NPC) is endemic in southeastern Asia, north Africa and southern China, with nearly 130,000 new cases globally in 2018, and 6% to 8% of these cases were *de novo* metastatic (1). Common metastatic sites of NPC are bone, lung, and liver, but brain metastasis is extremely rare. To date, only a few studies have reported leptomeningeal metastasis (LM) from NPC (2,3). LM has poor prognosis with an average 2–4 months survival (4), due to a lack of drugs which can penetrate blood–brain barrier effectively. Immune checkpoint inhibitor (ICI) was an

important treatment modality in different clinical settings of several cancers, and it was reported to improve intracranial response and survival in melanoma and non-small cell lung cancer (5,6). A phase II trial of pembrolizumab in patients with LM from solid tumors showed a 38% intracranial response at 12 weeks (7). However, the choice of further therapy after failure of ICI is a new challenge. Here, we report a 26-year-old man with *de novo* metastatic NPC who subsequently developed with LM after initial ICI treatment combined with chemoradiotherapy. We also review the diagnosis and treatment of LM, explore optional regimen after ICI failure. We present the following case in

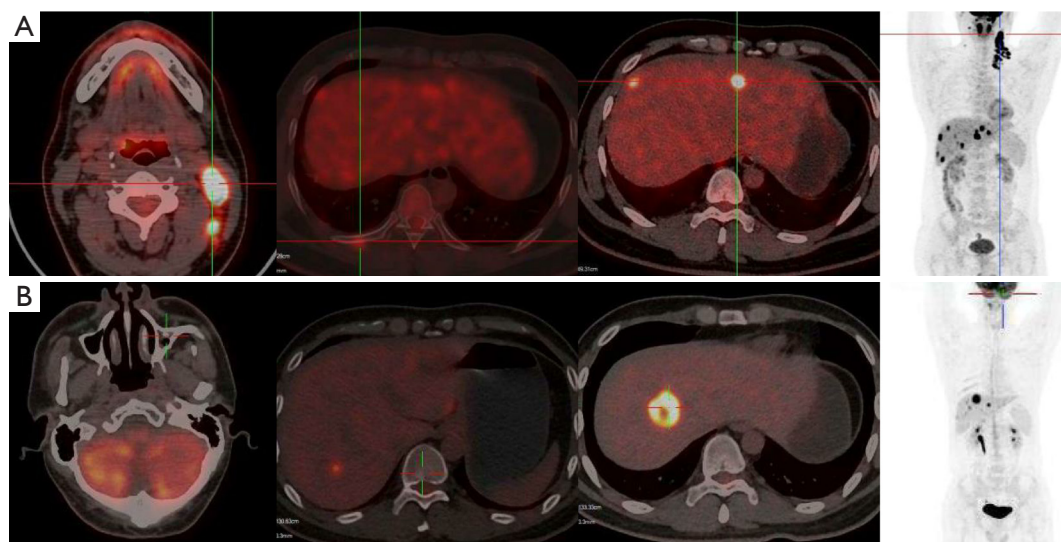


Figure 1 PET/CT scan at baseline (A) and one month after initial immune checkpoint inhibitor treatment combined with chemoradiotherapy (B).

accordance with the CARE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-1211/rc>).

Case presentation

A 26-year-old man from Chongqing City, China was diagnosed with nonkeratinizing undifferentiated carcinoma of the nasopharynx in December 15, 2020 on local hospital. He received four cycles of chemotherapy using TP (docetaxel and cisplatin) regimens but refused subsequent treatment. Then he was admitted to our hospital on June 4, 2021 with the complaint of left cervical masses again. He had no history of smoking or drinking. MRI was performed and showed thickness of posterior and bilateral nasopharynx. Retropharyngeal lymph nodes on the left side and bilateral cervical lymph nodes enlargement were also detected. Meanwhile, several enhanced brain lesions were revealed with maximum 0.8 cm in size. There was no recognized link between the lesions and nasopharynx. PET/CT scan was performed to show multiple liver metastasis and bone metastasis of the 9th right posterior costal (*Figure 1A*). Pathology immunohistochemistry consultation was nonkeratinizing undifferentiated carcinoma of the nasopharynx, Ki-67(+) 60%, EGFR(+), EBER(+). The level of Epstein-Barr virus deoxyribonucleic acid (EBV-DNA) titer was 472,000 copies/mL. Accordingly, the patient was diagnosed with nonkeratinizing undifferentiated carcinoma

of the nasopharynx (T2N3M1, stage IVB by the American Joint Committee on Cancer, 8th edition). He received three cycles of palliative chemotherapy with gemcitabine (1,000 mg/m² on days 1 and 8) and cisplatin (80 mg/m² on day 1), combined with three cycles of ICI camrelizumab (anti PD-1 antibody, 200 mg on day 1) intravenously every 3-week cycle. A partial response was demonstrated after three cycles of palliative treatment, but EBV-DNA bounced after undetectable. There was a Grade 4 thrombocytopenia, Grade 4 leukopenia, Grade 4 granulocytopenia and Grade 2 elevated transaminase after chemotherapy. Thereafter, he received definitive intensity-modulated radiotherapy (IMRT) to local and regional lesions (total dose of 70.4 Gy/32 F, 7 w) along with concurrent seven cycles of anti-EGFR antibody nimotuzumab (100 mg) every one-week cycle and three cycles of camrelizumab (200 mg) every 3-week cycle. EBV-DNA was still detectable during radiotherapy.

Two weeks after completion of radiotherapy, the patient experienced a transient unconsciousness, persistent fatigue and pain in both lower limbs. He was readmitted to our hospital on November 25, 2021. PET/CT scan was performed to show remission of nasopharynx lesions, cervical lymph nodes and bone metastasis (*Figure 1B*), without a second malignancy. But MRI revealed leptomeningeal linear enhancement, hydrocephalus and increased multiple intracranial metastatic lesions throughout both cerebral hemispheres (*Figure 2*). EBV-DNA titer

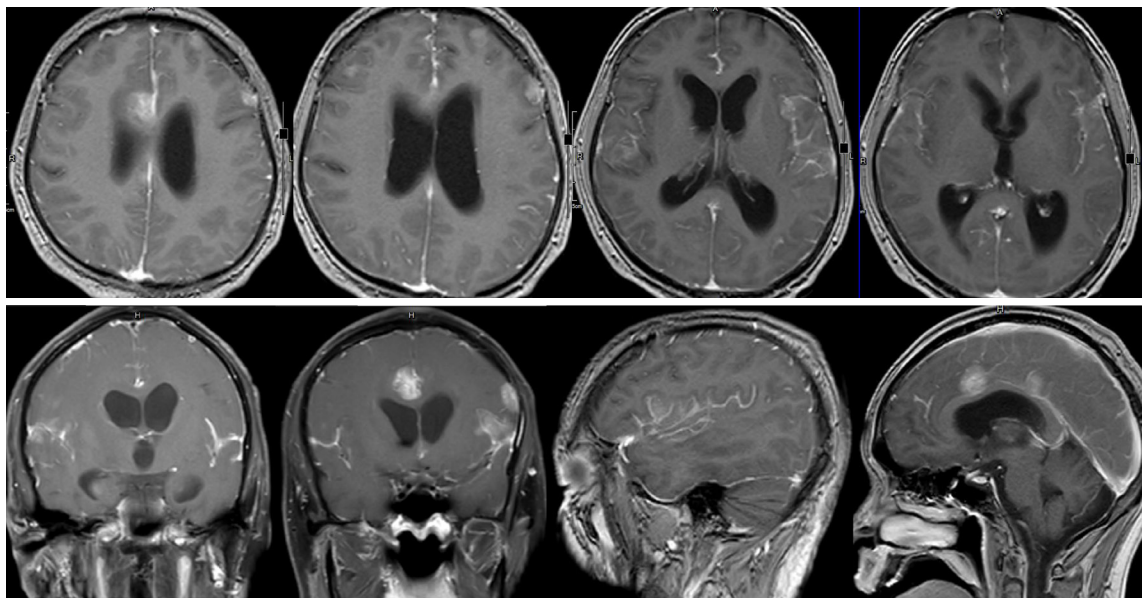


Figure 2 MRI of the leptomeningeal metastasis, hydrocephalus and multiple brain metastasis (T1 weighted contrast enhancement images).

raised. There was no evidence of meningeal irritation sign or infection. The presence of typical clinical features and an abnormal MRI was sufficient to make the diagnosis of LM, so the cerebrospinal fluid (CSF) wasn't detected. Due to the rapid progression of ICI treatment and unacceptable hematological toxicity on intravenous chemotherapy, the patient received oral concurrent capecitabine (1,000 mg/m², twice daily, d1–14) and palliative whole brain radiotherapy excluding brainstem and optic chiasm (total dose of 30 Gy/10 F, 2 w). The patient exhibited headache, nausea, vomiting and lower limbs weakness during radiotherapy, so mannitol and glucocorticoid were used to reduce intracranial pressure. Capecitabine then continued for a duration of three months. The clinical symptoms improved significantly with no intolerable adverse drug reactions. An MRI scan of the head showed that the original intracranial metastatic lesions and LM were almost completely gone (*Figure 3*). *Figure 4* shows the EBV-DNA titer during the courses of disease. The progression-free survival (PFS) was 5 months since the diagnosis of LM and the patient is ongoing follow-up examinations. *Figure 5* shows the whole timeline.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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.

Discussion

The incidence of LM typically varies by primary tumor type, occurring in about 5–15% of patients with hematologic malignancies and 5–8% of patients with solid tumors. The most common solid tumors are lung cancer, breast cancer, and melanoma (8). Though several studies reported multiple brain metastasis from NPC (9–11), there were rare reports of LM from NPC. To the best of our knowledge, our report demonstrates the first case LM from *de novo* metastatic NPC who was treated with initial ICI treatment combined with chemoradiotherapy.

Common symptoms and signs of LM include headache, confusion, nausea, vomiting, cranial nerve palsies, ataxia and cognitive impairment (8). The cytological demonstration of malignant cells in the CSF is the gold standard for the diagnosis of LM (12). A previous case reported that using imaging and plasma and CSF EBV DNA assays to diagnosis of LM (13). But the most common method is MRI of the brain which may reveal leptomeningeal enhancement with linear, irregular or nodular morphology. Hydrocephalus or subependymal deposits may also be seen (8). For the present case, the patient experienced transient unconsciousness,

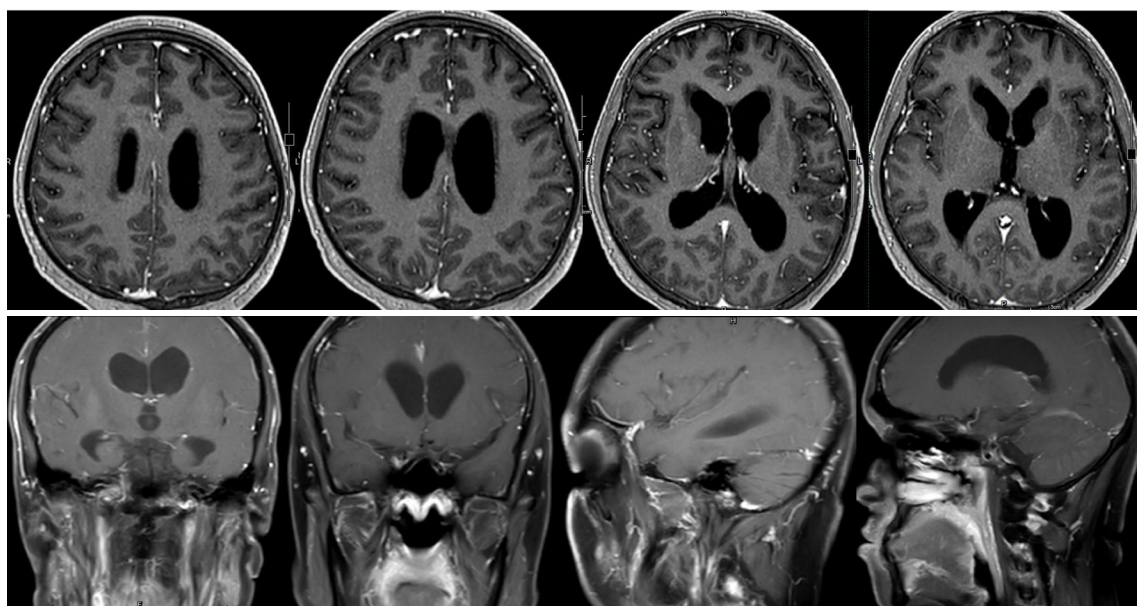


Figure 3 MRI of head at one month after whole brain radiotherapy combined with capecitabine (T1 weighted contrast enhancement images).

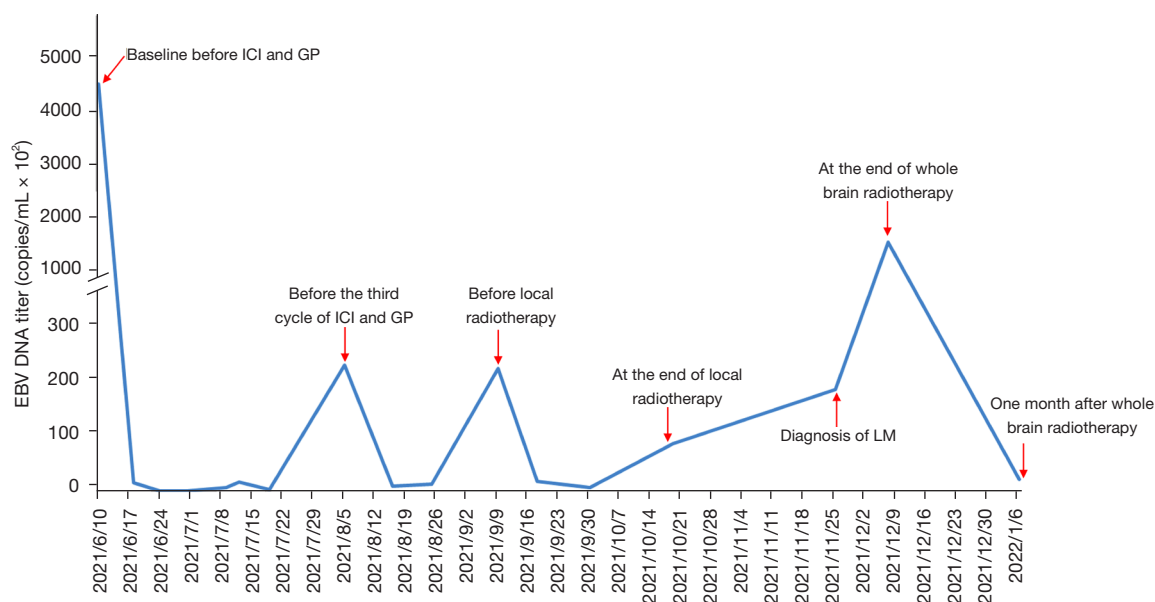


Figure 4 Longitudinal EBV-DNA titer during the courses of disease. The unit of EBV DNA levels was copies/mL × 10³. EBV, Epstein-Barr virus; ICI, immune checkpoint inhibitor; GP, gemcitabine and cisplatin; LM, leptomeningeal metastasis.

persistent fatigue and pain in both lower limbs. A second malignancy or brain abscesses could be excluded by PET/CT and laboratory results. The MRI of brain showed linear leptomeningeal enhancement in the brain fold and

hydrocephalus. In the presence of typical clinical features, an abnormal MRI is sufficient to make the diagnosis of LM, so the CSF wasn't detected.

For the present case, the patient was *de novo* metastatic

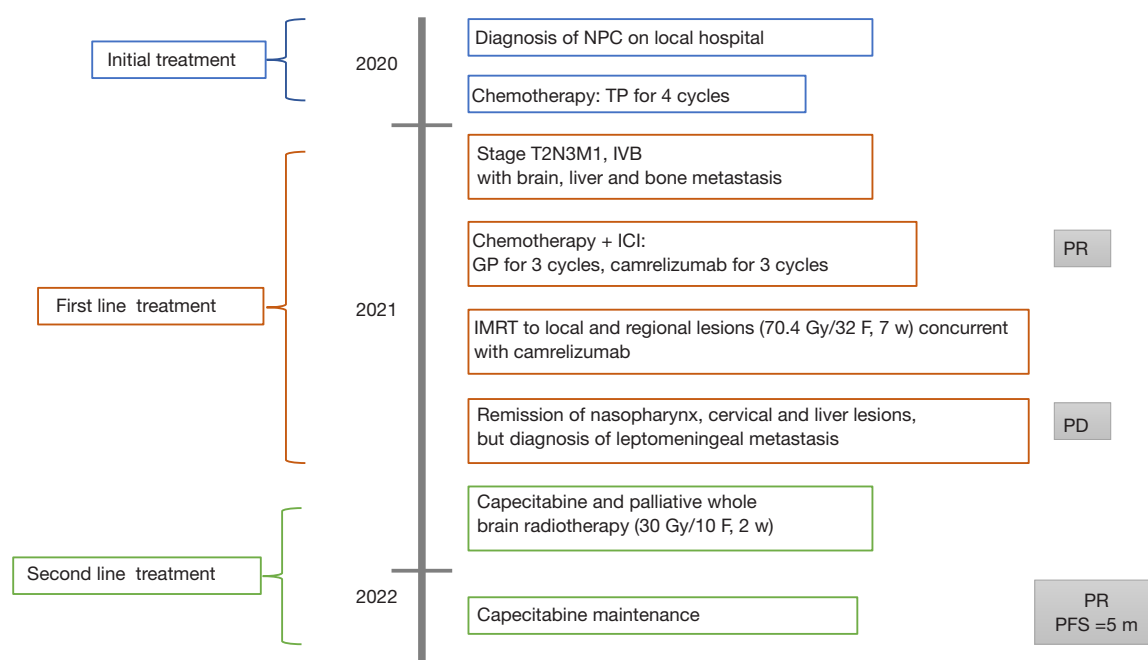


Figure 5 Timeline. NPC, nasopharyngeal carcinoma; TP, docetaxel and cisplatin; ICI, immune checkpoint inhibitor; GP, gemcitabine and cisplatin; IMRT, intensity-modulated radiotherapy; PR, partial response; PD progressive disease; PFS, progression-free survival.

NPC with multiple liver, bone and brain metastasis. He revived high-dose IMRT to the primary and nodal regions after palliative chemotherapy and immunotherapy. A multicenter phase 3 randomized clinical trial showed that local radiotherapy added to chemotherapy significantly improved survival in chemotherapy-sensitive patients with *de novo* metastatic NPC (14). Theoretically, endemic NPC was characterized by enriched lymphocytes infiltration and high PD-L1 expression, which makes ICI a promising treatment option (15). A randomized clinical trial showed that camrelizumab plus gemcitabine and cisplatin compared with placebo plus gemcitabine and cisplatin could significantly improve the PFS of recurrent or metastatic NPC in the first-line setting (16). Several studies also reported that ICI can improve intracranial response and survival in melanoma and non-small cell lung cancer (5,6). In addition, clinical trial and retrospective studies have proved the efficacy and safety of anti-EGFR antibody nimotuzumab in *de novo* metastatic NPC or recurrent/metastatic NPC (17-20). Though we used intensive comprehensive regimens, the patient progressed soon after initial anti PD-1 antibody treatment combined with chemoradiotherapy. Plasma EBV DNA titer at baseline and its dynamic change during chemoradiotherapy was strongly correlated with clinical

outcomes in patients with NPC (21). It was also reported that early clearance of plasma EBV DNA had longer PFS in patients treated with ICI (16,22). The patient in our case had a high EBV DNA titer at baseline and bounced after undetectable during initial ICI treatment combined with chemoradiotherapy, which might predict a worse prognosis. Because tumor microenvironment and PD-L1 expression of the patient were not identified, we could not get more information about immunotherapy resistance.

LM is a fatal complication of malignancies and has a worse prognosis than brain metastasis. As clinical trial data are paucity, treatment of LM is mostly guided by expert opinion. Whole-brain radiotherapy with doses 30–40 Gy/2–3 F is recommended for symptom management. Radiotherapy can reduce tumor volume, restore CSF flow and relieve hydrocephalus (23). A retrospective study included 519 patients with LM showed that chemoradiotherapy had the highest median overall survival than chemotherapy, radiotherapy alone, or best supportive care (5 vs. 3 vs. 3 vs. 1 month, $P < 0.001$) (24). The patient in our case obtained imaging and symptomatic relief after whole-brain radiotherapy. Though systemic chemotherapies can hardly penetrate blood-brain barrier, the blood-brain barrier is breakdown in condition of LM.

Several studies demonstrated the efficiency of capecitabine chemotherapy in patients with LM (25,26). In our case, oral capecitabine chemotherapy appeared to be efficient both intracranial and extracranial for the patient. Intrathecal chemotherapy is also optional without limitation of blood-brain barrier, but 47% of patients suffered from neurological complications (27). So the patient didn't receive intrathecal chemotherapy because of the relatively uncertain efficacy and frequent complication. A recent phase II trial showed the efficacy and safety of pembrolizumab in patients with LM from solid tumors, which conferred a 38% central nervous system response rate and a tolerable safety (7). Another similar phase 2 study of pembrolizumab in patients with LM had an overall survival rate of 60% at 3 months (28). A phase II study of 18 patients with LM receiving combined ipilimumab and nivolumab had overall survival rate of 44% at 3 months (29). However, the patient in our case suffered rapid intracranial progression after ICI treatment, so he didn't receive ICI treatment anymore.

As described above, chemotherapy plus ICI therapy has become the standard first line treatment in patients with metastatic NPC. There is a lack of data about the choice of further therapy after ICI failure. Recently, several studies suggested enhanced responses to chemotherapy following exposure to ICI in lung cancer (30-32). A study retrospectively analyzed 43 patients with recurrent/metastatic head and neck squamous cell carcinoma who progressed on ICI. The median PFS and OS on the subsequent chemotherapy or targeted therapy were 4.2 and 8.4 months respectively, which were higher than historical controls (33). Another retrospective study also showed that chemotherapy administered after ICI failure for metastatic urothelial cancer patients is a feasible treatment option (34). For the present case, the PFS on whole brain radiotherapy combined with capecitabine chemotherapy after ICI failure was at least 5 months.

In conclusion, LM from NPC is rare and with lethal characteristics. This report highlights the experience of diagnosis and treatment for LM from *de novo* metastatic NPC. We offered an alternative regimen that included whole brain radiotherapy, ICI and chemotherapy to treat the brain metastases. Additional study to investigate the appropriate treatment of brain metastasis and LM from NPC is warranted.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-1211/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-1211/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. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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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