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Original Article

Primary nasopharyngeal carcinoma with cerebrospinal fluid EBV positivity: A case report and mini literature review

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ABSTRACT

Background: To summarize the diagnosis and treatment of a patient with nasopharyngeal carcinoma and cerebrospinal fluid (CSF) Epstein-Barr virus (EBV) positivity (determined by next-generation sequencing), review the relevant literature, and explore the significance of EBV presence in the CSF of patients with nasopharyngeal carcinoma.

Methods: A patient presenting with headache as the initial symptom was diagnosed with nasopharyngeal carcinoma and admitted to the Eighth Medical Center of Chinese PLA General Hospital on March 3, 2021. Available databases were screened for reports on nasopharyngeal carcinoma with EBV-positive CSF and analyzed. The patients' general information, initial symptoms, treatment, and prognosis were subsequently evaluated.

Results: EBV-positive CSF is commonly observed in patients with recurrent nasopharyngeal carcinoma. However, no reports of EBV-positive CSF in patients with primary nasopharyngeal carcinoma have been published to date.

Conclusion: The presence of EBV in the CSF of patients with recurrent nasopharyngeal carcinoma is indicative of a poor prognosis. Thus, newly diagnosed nasopharyngeal carcinoma patients should undergo a lumbar puncture as soon as possible to have their CSF tested for EBV. Such a measure would promptly predict the prognosis and facilitate the development of a personalized treatment strategy.

1. Introduction

Nasopharyngeal carcinoma is one of the most common malignant tumors in China. According to the epidemiological data, the Chinese provinces of Guangdong, Guangxi, Hunan, Fujian, and Jiangxi have the highest incidences of nasopharyngeal carcinoma in the world. Factors related to host genetics, the environment, and EBV infection are the main causes of nasopharyngeal carcinoma, of which EBV infection is the most common factor [1]. Patients with initial symptoms such as headaches and cranial nerves involvement are usually admitted to the Department of Neurology and Ophthalmology. However, diagnosis and treatment are often delayed, meaning that by the time that the patient is finally referred to the Otolaryngology Department their disease has considerably progressed.

The presence of EBV in the cerebrospinal fluid (CSF) of patients with nasopharyngeal carcinoma is rarely reported. In particular, there have been no reports of patients with primary nasopharyngeal carcinoma and EBV-positive CSF. In this report, we present such a case. The patient, who initially experienced a headache and double vision, did not respond to treatment with symptomatic analgesia and nerve blocks administered at other hospitals. After being admitted to our hospital at a later stage of disease, the patient underwent a contrast-enhanced head MRI scan, which revealed lesions in the left posterior wall of the nasopharynx. The patient was later diagnosed with nasopharyngeal carcinoma according to the histopathologic biopsy results. mNGS of the patient's CSF sample revealed that they increased levels of EBV DNA sequences. After radiotherapy, the patient's headache greatly improved. In this manuscript, we present a case of a patient

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with nasopharyngeal carcinoma and EBV-positive CSF, in addition to briefly reviewing the relevant literature.

2. Clinical data

A 52-year-old female, who was hospitalized on March 3, 2021, due to experiencing a headache for 1 year and double vision for 10 months. The headache was characterized by a throbbing or shooting pain localized to the left supraorbital and temporo-occipital areas. The recurrent pain lasted for periods ranging from a few hours to 2 days and could be spontaneously relieved. The patient had double vision for 10 months before admission (May 2021) and had no apparent abnormality in the head MR examinations at other hospitals. The patient was treated with drugs, including sustained release ibuprofen, pregabalin, Toutongning, and flunarizine hydrochloride capsules, and had received therapeutic nerve blocks; however, none of these methods alleviated the symptoms.

The patient had a 10-year history of Sjogren's syndrome, which was treated with oral methylprednisolone and *Tripterygium wilfordii* for the first 7 years. The patient's visual analogue scale (VAS) score upon admission was 8–9. The nervous system examination showed that the patient was conscious, articulate, and had normal cognitive ability. The abduction movement of left eye was limited. Double vision occurred when both eyes focused to the left. Physical examination of the residual cranial nerves revealed no abnormalities. Muscle strength and limb tension were also normal. The patient had exhibited coordinated bilateral ataxic movements, and her bilateral tendon reflexes were symmetrical and normal. Moreover, the patient's bilateral pathological signs and meningeal stimulation signs were negative.

The following examinations also revealed no abnormalities: routine blood, biochemistry, coagulation function, D-dimer, and infection (hepatitis A, hepatitis B, hepatitis C, gonorrhea, tuberculosis, AIDS, syphilis, and hepatitis E). The ESR was 43 mm/h. A full panel of tumor markers was performed: CA 211 4.24 ng/mL (normal range: 0–4.0), B2-MG 3.53 μg/mL (normal range: 0–3.04), and FE 276.3 ng/mL (normal range:13–150). The rest of the indexes were in the normal range. Thyroid function was assessed: TSH 4.8 μIU/mL (normal range: 0.27–4.2), TG 1.79 ng/mL (normal range: 3.5–77), anti-TPO 499.9 IU/mL (normal range: 0–34). The initial pressure of the CSF obtained through a lumbar puncture was 105 mmH_2O. The total cellular score was 6×10^6 cells/L and the white blood cell count was 6×10^6 cells/L. CSF cytology revealed the occasional presence of lymphocytes but no tumor cells. The amino acid concentrations were: Pro 0.21 g/L, Glu 2.95 mmol/L, and Cl 112.71 mmol/L. CSF mNGS detected 31 human herpesvirus type 4 (EBV) sequences.

The contrast-enhanced MR images revealed no abnormal enhancement in the brain parenchyma and meninges. The soft tissue mass located on the left posterior wall of the nasopharynx showed an isometric T1, a slightly shorter T2, and a slightly higher FLAIR sequence, suggesting the uneven enhancement of a lesion measuring 3.2×2.9 cm. The involved bone of the left margin of the slope was obviously enhanced. The result suggested that the patient had nasopharyngeal carcinoma, with partial skull base bone and left cavernous sinus involvement. The tumor enveloped the left petrous internal carotid artery and the cavernous sinus segment; additionally, the bilateral cervical lymph nodes were enlarged (Fig. 1). The head MRA revealed that part of the left intracranial artery (petrous internal carotid artery, cavernous sinus segment) was slightly thinner than normal, which was thought to be caused by these vessels being encased by a cell mass (Fig. 2). The chest CT showed multiple areas of mild lymph node enlargement in the mediastinum, at the base of the neck, around the clavicle, in the axilla, and the cardiophrenic angle. A few small nodules (< 5 mm in diameter) were found in the middle lobe of the right lung, posterior basal segment of right inferior lobe, and lateral basal segment of the left inferior lobe; some of these nodules were calcified. Moreover, the bilateral pleura was partially thickened and calcified. The nasopharyngeal CT revealed that the left pharyngeal recess had disappeared; moreover, the left nasopharyngeal posterior outer wall mass appeared as a slightly low-density focus. A biopsy of the nasopharyngeal lesions was performed at the Department of Otorhinolaryngology; the pathology indicated poorly differentiated squamous cell carcinoma. Paraffin tissue EBV situ hybridization revealed that the patient was EBER-positive (Fig. 3). The patient was subsequently transferred to the cancer hospital. After radiotherapy combined with targeted therapy, the patient's headache was significantly alleviated; however, the double vision symptom remained unchanged.

3. Discussion

EBV, also known as human herpes virus type 4, belongs to the *Herpesviridae* family of DNA viruses. EBV infection is highly prevalent in humans. Because EBV infects B lymphocytes and epithelial cells, EBV infection is associated with autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjogren's syndrome [2]. These diseases are potentially caused by the chronic or repeated infection of epithelial cells by EBV, the cross-reactive immune response triggered by B lymphocytes, or autoimmune deficiencies. Chen et al. found that the EB nuclear antigen (NA-1) IgA antibody (EBNA-1-IgA) was significantly more seroprevalent in individuals with dermatomyositis, polymyositis, SLE, or nasopharynx cancer compared with

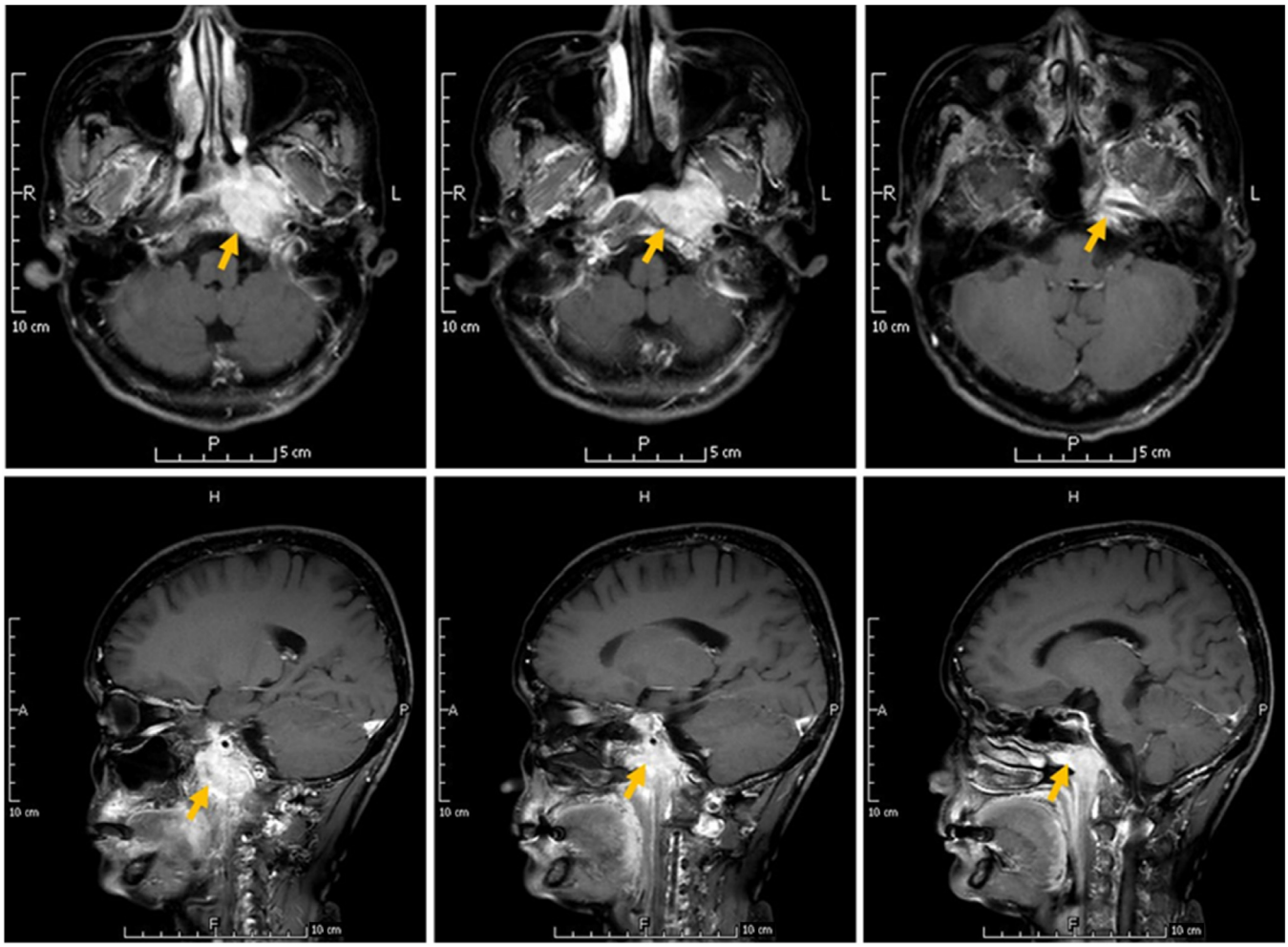

Fig. 1. The head MRI scan showing T1 enhancement and the uneven enhancement of the lesions on the left posterior wall of the nasopharynx, with partial skull base bone and left sinus cavernosus involvement. The left petrous internal carotid artery and the cavernous sinus segment were enveloped by the tumor mass. The bilateral cervical lymph nodes were also enlarged.

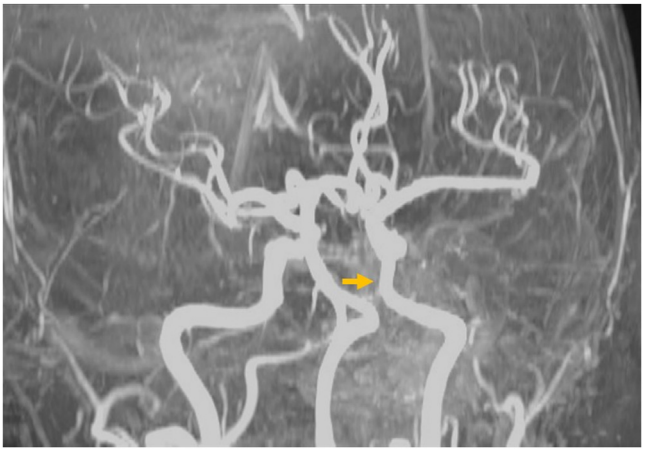

Fig. 2. Head MRA showing that the left petrous internal carotid artery and the cavernous sinus segment were thinner on one side than the other, indicative of a lump encasing them.

those with non-malignant tumors and healthy controls [1]. The levels of IgM, IgG, and IgA targeting EBV early antigen/diffuse (EA/D) are also significantly increased in the serum of SLE patients [3], indicating that immunocompromised individuals are especially susceptible to EBV infection. The activation, replication, and cleavage of EBV, in turn, promotes immune cross-reactivity, potentially contributing to the progression of autoimmune diseases.

It has been suggested that anti-Ro-antibody-producing B cells observed in patients with Sjogren's syndrome are implicated in EBV infection; moreover, early EBV antigens are more likely to appear in the serum of Sjogren's syndrome patients [4]. The patient in our study had a history of Sjogren's syndrome and took oral immunosuppressants. It is possible that EBV, which remained latent in the patient's nasopharyngeal epithelial cells, was activated in the immunosuppressed state. The replication of EBV subsequently promoted the transformation of epithelial cells into cancer cells. Recent studies have shown that EBV may also participate in and promote the occurrence and development of some neurological diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, acute disseminated encephalomyelitis, brain tumors, encephalitis and meningitis, and acute cerebellar ataxia

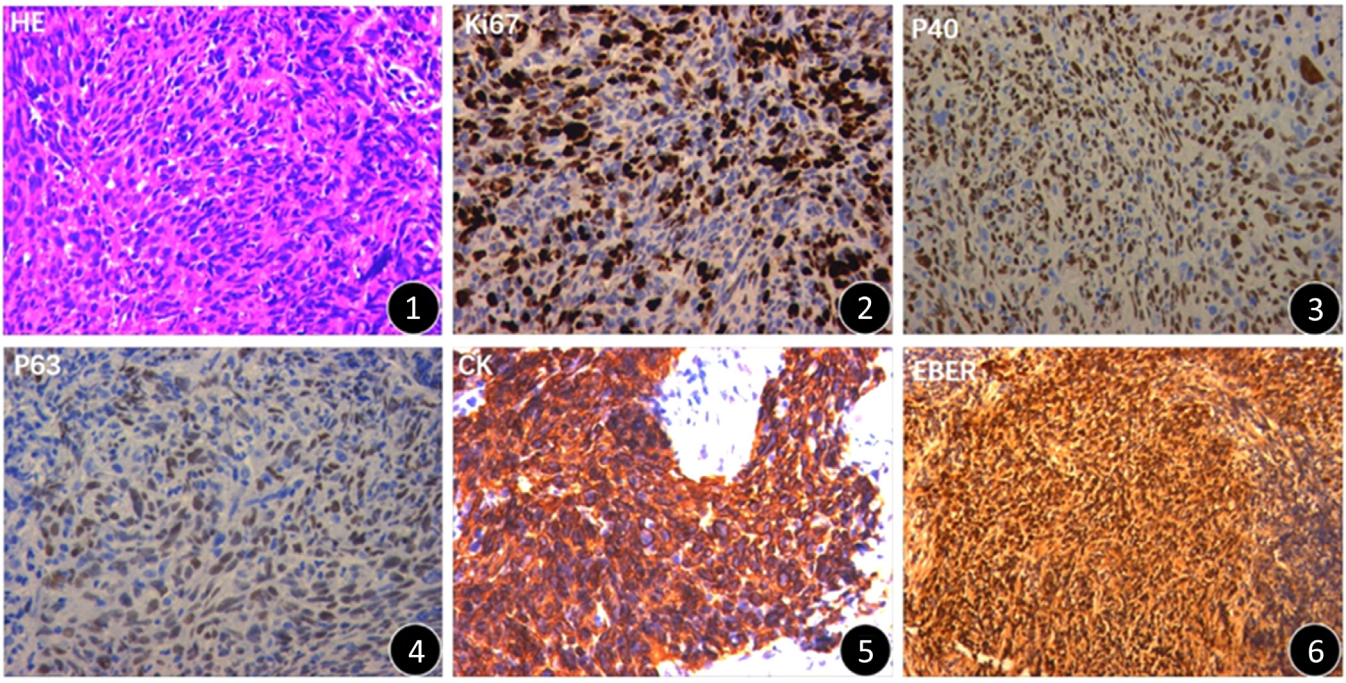

Fig. 3. Nasopharyngeal lesion biopsy results. 1. hematoxylin-eosin staining. 2. Ki67 staining. 3. P40 staining. 4. P63 staining. 5. CK staining. 6. Paraffin-embedded tissue EBER staining (200 × magnification).

[5]. In addition, EBV infection is highly associated with some neoplastic diseases, such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, and nasopharyngeal cancer.

EBV positivity in the CSF is commonly observed in conditions such as EBV-infection-associated encephalitis and meningitis, where it is often associated with a poor prognosis [6]. In the present study, mNGS of the patient's CSF detected 31 EBV sequences. We wondered whether this EBV positivity was due to EBV infiltration into the brain or EBV-associated meningitis. Alternatively, we speculated that it could be the result of meningeal invasion by cancer cells, which would damage the blood-brain barrier and allow the virus to enter the brain. It is generally considered that the number of EBV sequences below 10 is considered for colonization. Huang et al. reported one adult case of EBV meningoencephalitis. mNGS identified 157 EBV sequences in the patient's CSF [7], which was much higher than that detected in our patient. The other patient showed no symptoms of intracranial infection, such as fever, seizures, or high cranial pressure; their CSF cell counts and protein levels were also normal [7]. Therefore, the patient was not diagnosed with EBV encephalitis or meningitis, even though the EBV sequence number in their CSF was relatively high. It is possible that, in the patient with nasopharyngeal carcinoma, the dormant EBV may have been activated to replicate in or invade the meninges, causing damage to the blood brain barrier, allowing the virus to enter the brain. Meiyin et al. [8] reported another patient with recurrent nasopharyngeal carcinoma, whose blood and CSF tested positive for EBV DNA. Although tumor cells were not detected by cytology, the patient still exhibited leptomeningeal metastasis of nasopharyngeal carcinoma. Until now, there have been no reports of patients primarily diagnosed with nasopharyngeal carcinoma who tested positive for EBV DNA in their CSF.

Although a headache is a symptom in 35%–50% of nasopharyngeal carcinoma patients, the number of patients who reported a headache as their initial or only symptom was much lower [9]. Lee et al. conducted a retrospective analysis of 4768 patients with nasopharyngeal carcinoma and found that 34.8% of patients had headaches; however, among them, only 0.3% or 3.7% had a headache as the only or first symptom [10]. Therefore, a large proportion of nasopharyngeal carcinoma patients may be misdiagnosed in the early stages of disease. Indeed, our patient sought consultation from the Neurology and TCM Departments of many hospitals without obtaining a clear diagnosis. The head MRI data taken at other hospitals 1 year prior, revealed a small mass on the left side of the patient's nasopharynx, measuring approximately 1 cm × 0.5 cm. This mass had slightly longer T1 and shorter T2 signals. Remarkably, both the nasopharyngeal and skull base abnormalities were overlooked by the Radiology Department of previous hospitals. Upon admission to our hospital, the patient underwent an enhanced head MRI, which revealed a significant enlargement of the lesion and its invasion into the skull base. The patient's CSF indicators were within the normal range, no cervical lymph node enlargement was observed on ultrasound, and no intracranial metastasis was detected on cranial enhancement MRI. Given that a headache may be caused

by early cancer cell invasion, possibly complicated by infection, cervical lymph node metastasis, skull base bone destruction, and intracranial invasion, we speculate that the headache might have been due to the destruction of the skull base bone and meningeal invasion.

As a result of tumor cell invasion, the adjacent anatomical structures of cavernous sinus, including the cranial nerves and the internal carotid artery, may have been involved. Common clinical cranial nerve involvement typically relates to the V and VI cranial nerves. In this case, the patient experienced double vision and limited abductions of the left eye after taking two boxes of pregabalin capsules in the tenth month following headache onset. Although the medication leaflet stated that diplopia and extraocular paralysis were potential adverse reactions of pregabalin, the above symptoms were not listed. Huang et al. conducted a search of 73 ADR cases reported between December 2004 and May 2017; among these, only one patient had diplopia [11]. In our study, cranial enhanced MRI scans indicated involvement of the left cavernous sinus, located close to the abducens nerve. Even after pregabalin was stopped, the patient's double vision symptoms did not improve; this was likely associated with the intracranial invasion of the abducens nerve by the nasopharyngeal carcinoma. Nasopharyngeal carcinoma is not only capable of invading the cranial nerve and blood vessels but can also affect the brain parenchyma. Yang Long et al. analyzed data from 17 nasopharyngeal carcinoma patients with headaches, dizziness, and cranial nerve dysfunction. They found one case which involved the invasion of the pons lateral visual center and medial longitudinal fasciculus; this patient also developed "one-and-a-half syndrome" at a later stage. Another patient was initially admitted to the Rheumatology Department due to limb weakness and was diagnosed with dermatomyositis. This patient was subsequently transferred to the Neurology Department due to bucking and was eventually diagnosed with nasopharyngeal carcinoma [12]. The contrast-enhanced head MRI of this patient showed invasion and envelopment of the petrous internal carotid artery and the cavernous sinus segment; however, no corresponding clinical symptoms were evident.

Leptomeningeal metastasis caused by nasopharyngeal carcinoma is extremely rare. The local diffusion of tumor cells is a possible mechanism of meningeal invasion. Ma et al. have summarized five cases of nasopharyngeal carcinoma with meningeal involvement. They believe that when CSF cytology is negative, CSF and plasma tests for EBV DNA can complement neuroimaging examination to confirm leptomeningeal metastasis [8]. Our patient was pathologically diagnosed with low-differentiated squamous cell carcinoma. Contrast-enhanced head MRI data showed no evidence of enhanced meninges. CSF cytology was negative whereas CSF was EBV-DNA-positive, suggesting possible leptomeningeal metastasis of nasopharyngeal carcinoma. Therefore, patients suspected of having nasopharyngeal carcinoma should undergo mNGS for EBV DNA in the CSF. Such a measure will help determine the prognosis and risk stratification of patients, leading to the development of a more personalized treatment plan [13].

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Author contributions

J.L.F.: Concept, Study design, Writing draft. S.W.: Sample collection and processing, Data analysis, Writing–original draft. H.L.Z.: Sample collection and processing, Data analysis. J.Z.: Approval of the study, Editing and approval of the final manuscript. X.L.W.: Study design, Supervision, Approval of the final manuscript. J.L.F. and S.W. have contributed equally to this work and share first authorship.

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Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data available statement

Not applicable.

Ethics statement

None.

Informed consent

Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images.

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