Yonago Acta Medica 2021;64(3):318–323 doi: 10.33160/yam.2021.08.009

A Case of Gorham-Stout Disease Treated with Fistula Closure by Transmeatal Approach

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ABSTRACT

Gorham-Stout disease, a rare and intractable disease of unknown etiology, causes systemic bone lysis and replacement with lymphoid tissue. Here, we report a case of Gorham-Stout disease with cerebrospinal fluid leakage in a 16-year-old boy. The patient complained of nasal discharge, right ear obstruction, fever, and headache. A computed tomography scan of the head showed osteolysis around the right internal carotid artery, vestibule, and cochlea and osteolytic changes in the left parietal bone. It was suggested that the patient had bacterial meningitis owing to the leakage of cerebrospinal fluid from the fistula caused by the temporal bone osteolysis. He was treated with meropenem, and a transmeatal fistula closure and a bone biopsy of the left parietal bone were performed. Intraoperatively, osteolysis was observed on the promontory and around the internal carotid artery. The fistula was closed by dense filling and compression around the fistula, in the middle ear cavity, and in the external auditory canal. The symptoms disappeared after the surgery. Bone biopsy showed the presence of a lymphangioma, and Gorham-Stout disease was diagnosed. Prophylactic bisphosphonate therapy was initiated. A 4-year follow-up revealed no progression of the disease.

Key words bacterial meningitis; cerebrospinal fluid leakage; fistula closure; Gorham-Stout disease; osteolysis

Gorham-Stout disease (GS), a rare disease of unknown etiology, causes systemic bone lysis and replacement with lymphoid tissue. It is designated as an intractable disease in Japan, and no effective treatment has been established. In the head and neck region, osteolysis around the inner ear causes perilymphatic fistulas and cerebrospinal fluid (CSF) leakage. Perilymphatic fistulas cause complications, such as deafness and vertigo or dizziness, which are directly related to the patient's quality of life, and CSF leakage could lead to meningitis, a potentially fatal complication. Since it is difficult to cure the disease, symptomatic treatment must be instituted. However, surgery is one of the most effective treatment methods, albeit with lower long-term efficacy. In this article, we aimed to report a case of GS disease with CSF leakage that was treated with fistula closure using a transmeatal approach and to describe the patient's subsequent progress.

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Received 2021 June 7
Accepted 2021 July 20
Online published 2021 August 24
Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; GS, Gorham-Stout disease; MRI, magnetic resonance imaging; mTOR, mechanistic target of rapamycin

PATIENT REPORT

The patient was a 16-year-old boy with a history of bacterial meningitis at the age of 13 years. No relevant family history was noted. The patient was admitted to a hospital after he developed fever and headache, following a two-day history of a nasal discharge and right ear obstruction. A CSF analysis revealed a cell count of 159 cells/μL. Therefore, viral meningitis was suspected. After the fever persisted, a second CSF examination on the fourth day of hospitalization revealed an elevated cell count of 544 cells/μL. Additionally, a glucose test around the pharyngeal opening of the Eustachian tube was positive, and CSF rhinorrhea was suspected. A computed tomography (CT) scan of the head showed osteolysis around the right inner ear canal and an isodense area in the tympanic cavity. It was suggested that the patient had bacterial meningitis due to CSF leakage, and meropenem therapy (2 g every 8 h) was initiated. The fever resolved, but the rhinorrhea persisted, thus the patient was transferred to our hospital for treatment on the 13th day of hospitalization.

The tympanic membrane of the right ear was swollen, and there was clear effusion in the tympanic cavity. CSF analysis revealed a decreased in cell count (25 cells/μL, polymorphonuclear cells: 4%) compared to the pre-treatment count. The CSF cultures were negative (Table 1). Bone marrow examination revealed no evidence of hematologic tumors that could cause osteolytic lesions. A CT scan of the temporal bone showed osteolysis around the right internal carotid artery, vestibule, and cochlea, as well as osteolytic changes in the left parietal bone. Although there was fluid in the mastoid cavity, no evidence of destruction was found within

Table 1. Cerebrospinal fluid findings

The number of days since hospitalization	1	4	13	25
Opening pressure (mmH_2O)	140	120	NA	100
Cell count/μL	159	544	25	9
Polymorphonuclear cells (%)	96	58	4	0
Protein (mg/dL)	NA	59	39	NA
CSF to serum glucose ratio	0.65	0.53	0.59	NA
Culture	NA	Negative	Negative	NA

CSF, cerebrospinal fluid; NA, not available.

the mastoid process (Figs. 1A, B and D). T2-weighted magnetic resonance imaging (MRI) of the head exhibited relatively hyperintense areas around the right pericarotid canal, vestibule, cochlea, and the left parietal bone, which were seen as bone defects on the CT scan, suggesting osteolysis (Figs. 1C and E). A whole-body CT scan with contrast enhancement and radiography of the pelvis and extremities showed no osteolysis, and there was no pleural effusion or interstitial change in the lungs. In addition, there were no abnormal findings in the spleen or liver. Cerebrospinal scintigraphy using 111In-diethylenetriaminepentaacetic acid (^{111}In-DTPA) showed increased accumulation in the region corresponding to the right mastoid, suggesting CSF leakage (Fig. 2).

We suspected GS disease based on the multiple, progressive, osteolytic changes seen on imaging. Therefore, we planned to close the CSF leakage, and at the same time, conduct a biopsy to exclude other diseases.

The patient was treated for meningitis with meropenem. After treatment for meningitis, the right transmeatal fistula closure was performed to prevent CSF leakage on day 29 of hospitalization. At the same time, a biopsy of the left parietal bone was performed to investigate the cause. The surgical approach was taken through a post-auricular incision. The subcutaneous connective tissue of the temporal region was harvested to use as an obstructive material for the fistula. A tympanomeatal flap was raised to check the inside of the tympanic cavity. Osteolysis was observed on the promontory and around the internal carotid artery. There was evidence of the pulsatile leakage of CSF in the middle ear. The fistula was obstructed with connective tissue and cartilage fragments of the cymba and was fixed with fibrin glue. In addition, the tympanic cavity was filled with cellulose sponge to prevent leakage, and the external auditory canal was densely filled with cellulose sponge to provide additional transmeatal pressure (Fig. 3).

The pathological findings in the biopsied parietal bone showed multiple large and small dilated vascular-like structures in the bone lined by a single layer of endothelial-like cells (Fig. 4). D2-40 immunostaining was positive, although only partially, confirming the presence of lymphatic endothelial cells. Based on the clinical and pathological findings, the patient was diagnosed with GS disease. The symptoms of nasal discharge disappeared after the surgery, The administration of meropenem was discontinued on the second postoperative day, and treatment with sodium risedronate was started to control the progression of GS disease. As part of the follow-up, a whole-body CT scan was performed every year until the third postoperative year, and we continue to perform a temporal bone CT scan every year. Four years have passed since the surgery, and the patient is leading a normal life with no new findings related to osteolysis and no recurrence of CSF leakage.

DISCUSSION

GS disease was first described by Gorham et al. in 1955 as a disease causing "disappearing bones."[1] The disease is characterized by progressive osteolysis throughout the body, causing pain and bone fractures. It is also associated with lesions in the lungs, spleen, and other viscera and with a variety of symptoms depending on the affected organ. The pathogenesis of GS has not yet been elucidated, although it is thought that the osteolysis may be caused by mechanical compression of the bone owing to lymphatic hyperplasia or by the activation of osteoclasts by various factors.[2, 3] Disease onset most commonly occurs in young age groups, but it has been reported across all age groups. To date, approximately 100 cases of GS disease have been reported in Japan, including those with lymphangiomas.

Poor prognosis is associated with chest lesions, such as those caused by pleural effusion or chylothorax, but the prognosis for patients without chest lesions is good.[4] However, it is impossible to predict whether the

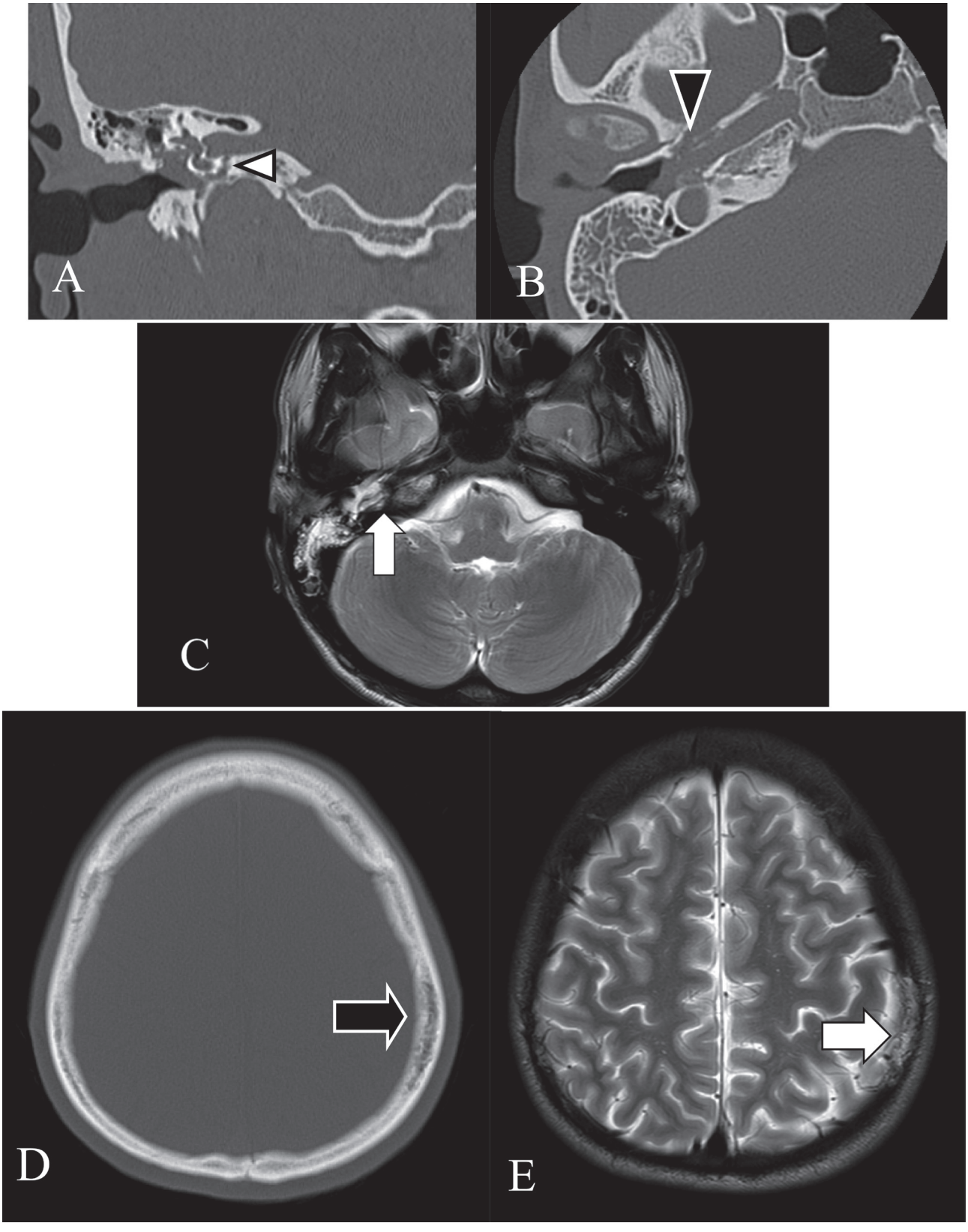

Fig. 1. A, **B**, **D**: CT scan images of the temporal bone. **C**, **E**: MRI scan image. **A**: Osteolysis around the cochlea. The white arrowhead indicates osteolysis of the internal auditory canal. **B**: The black arrowhead indicates osteolysis around the internal carotid artery. There is fluid in the mastoid cavity. **C**: White arrow: The area around the right carotid artery periphery, vestibule, and cochlea showing relatively high signal intensity on T2-weighted MRI. **D**: Hypodense region of the left parietal bone (black arrow). **E**: White arrow: The left parietal bone showing a high signal intensity area on T2-weighted MRI. CT, computed tomography; MRI, magnetic resonance imaging.

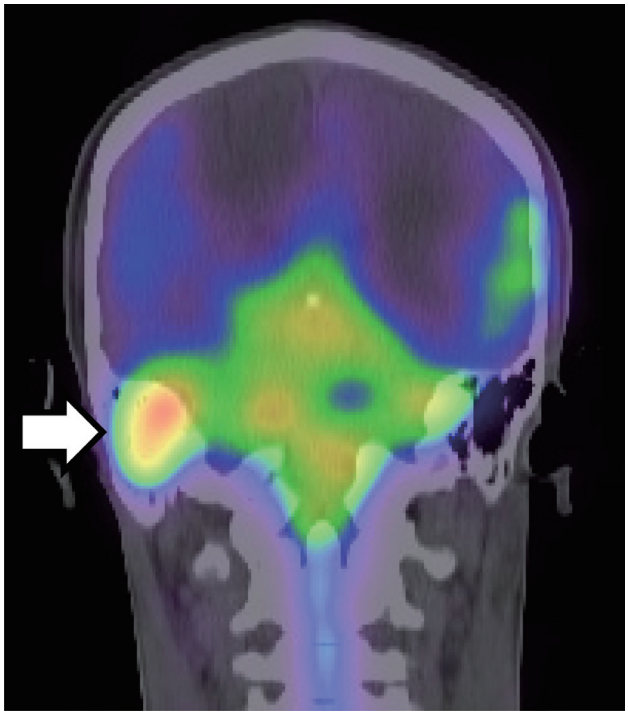

Fig. 2. Cerebrospinal scintigraphy using ^{111}In-DTPA. White arrow: An increased accumulation in the area corresponding to the right mastoid, suggesting CSF leakage. ^{111}In-DTPA, 111In-diethylenetriaminepentaacetic acid; CSF, cerebrospinal fluid.

disease will resolve spontaneously or progress.

The main findings are as follows: a) localized or scattered lysis of the bone cortex or marrow; b) diffuse lymphangiomatous lesions or lymphatic effusion in the intrathoracic organs, such as the lungs, mediastinum, and heart; and c) diffuse lymphangiomatous lesions or lymphatic effusion in the intraperitoneal organs, such as the liver and spleen. Diagnosis can be confirmed when one or more of these three criteria are met, and when the pathological examination reveals irregularly dilated lymphoid tissue lined by lymphatic endothelium. In some cases, spindle-shaped cells are present. Conversely, a diagnosis can also be confirmed when all other possibilities in the differential diagnosis (malignant neoplasm, congenital osteolytic disease, etc.) can be ruled out. Bone lesions can be diagnosed by radiography or CT, but changes in the bone marrow and the spread of the disease to the soft tissues should be confirmed by T2-weighted MRI. High-resolution CT and MRI are also useful for the evaluation of thoracic lesions.

Interferon,[5] bisphosphonates,[6] propranolol,[7] bevacizumab (anti-vascular endothelial growth factor therapy humanized monoclonal antibody),[8] and mechanistic target of rapamycin (mTOR) inhibitors[9] have been reported as drug therapies, but none have been established. Sirolimus, an mTOR inhibitor, is expected to be a new therapeutic agent, but it is still in the clinical trial stage in Japan and cannot be used easily.[9] In addition, surgical treatment, radiotherapy, and a local injection of OK-432 have been reported as treatments for local lesions.[10, 11] In particular, there are reports on the treatment of pathological fractures by, repair, fixation, and bone grafting.[12]

In this case, the osteolysis in the right temporal bone and left parietal bone was used to differentiate the disease, and tissue biopsy was performed to confirm the diagnosis. Fistula closure with a surgical approach

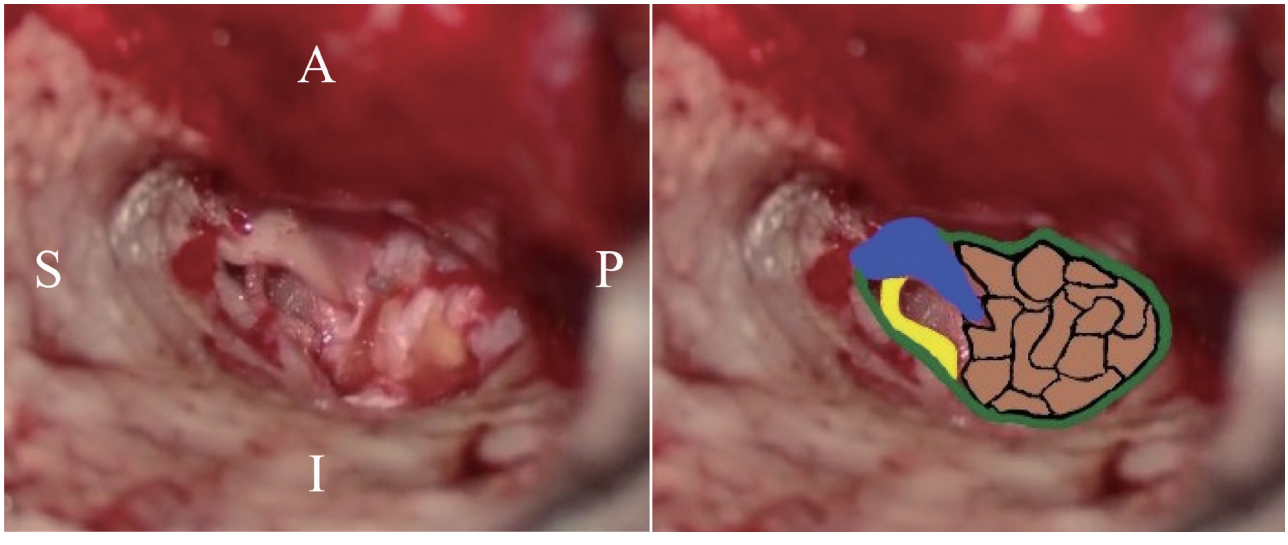

Fig. 3. Intraoperative findings. Left: Intraoperative photograph. Right: Illustrative intraoperative photographs. Cartilage fragments, connective tissue, and cellulose sponges filled in the tympanic cavity. A: anterior, P: posterior, S: superior, I: inferior. Blue:the malleus, yellow: chorda tympani, brown: connective tissue and cellulose sponge, green: annulus tympanicus.

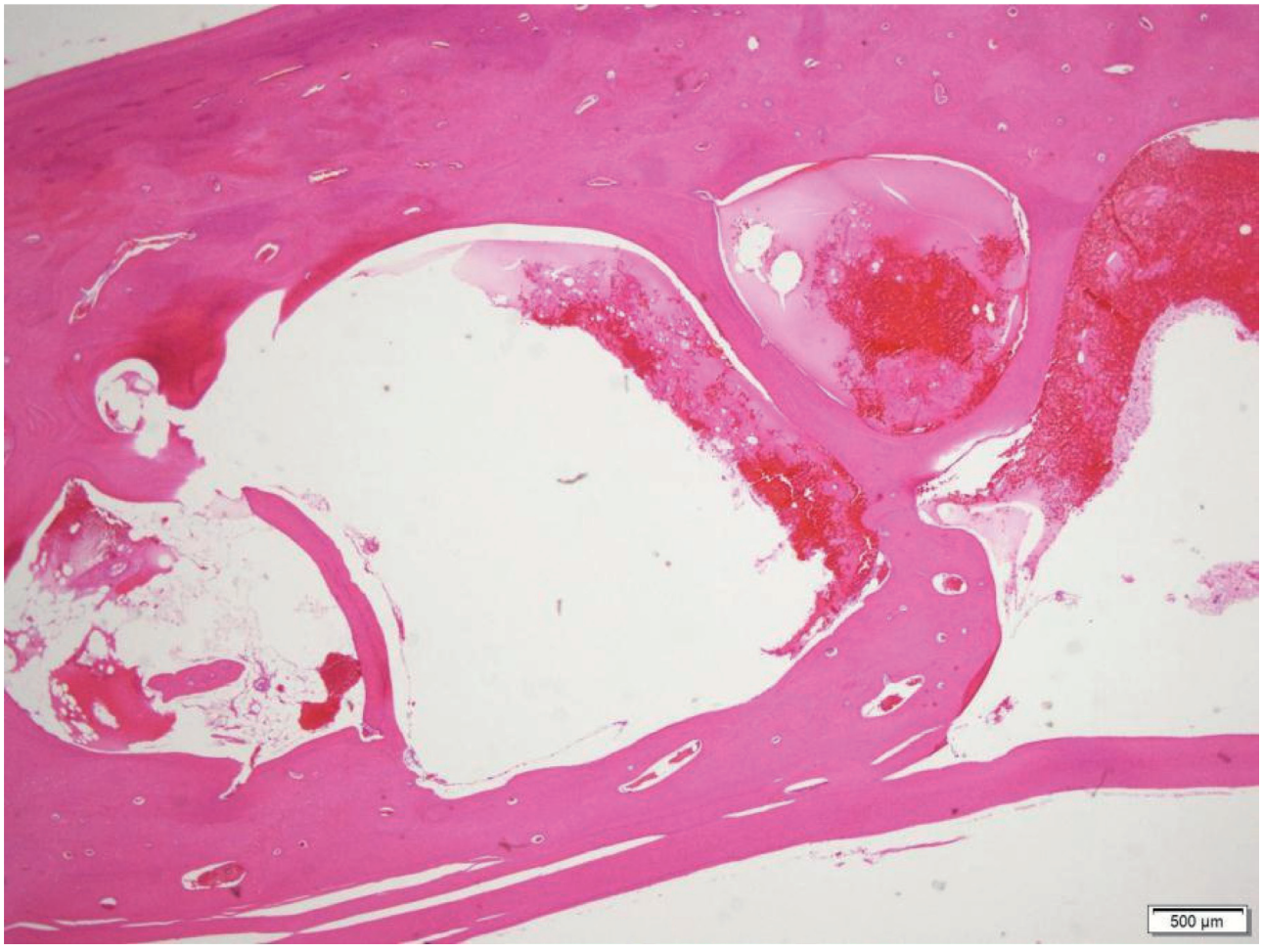

Fig. 4. Histopathological findings of the left parietal bone. There are many large and small dilated vascular structures in the bone, and the inner surface is lined with endothelial-like cells (hematoxylin eosin staining). Bar = 500 μm.

is considered essential for local control of persistent CSF leakage. The subcutaneous tissue of the temporal region, cartilage fragments, and cellulose sponges were used to tightly fill and compress the periphery of the fistula, the middle ear, and the external auditory canal. This allowed us to achieve closure without recurrence after the surgery. Other authors have reported closure of the fistula by using intratympanic fat filling and a Eustachian tube plug or by using fascia and periosteum in the middle cranial fossa approach.[13, 14] In all of these reports, the patients progressed without relapses, therefore, the conventional methods of dealing with CSF leakage seem to be effective. Surgical closure of CSF leakage can be achieved using either the transmeatal or the middle cranial fossa approach. The middle cranial fossa approach is more invasive, and there is a risk of complications, such as seizures, loss of hearing, facial palsy, and infection.[15] Therefore, we first adopted the less invasive and risky method of fistula closure with the transmeatal approach. The advantage of this approach is that when the area to be filled is small, a sufficient amount of filling material can be obtained from the same surgical site. In addition, the additional pressure from the external auditory canal with cellulose sponges may have contributed to some extent in reducing the CSF leakage, and we thought this would be an effective approach to try as an initial surgery. In this case, if the osteolysis around the inner ear had progressed, and there had been a recurrence of CSF leakage, it would have been difficult to perform an additional fistula closure from the side of the tympanic cavity. In such cases, it is necessary to consider another approach, such as the middle cranial fossa approach. In addition, bisphosphonates were used to prevent the progression of the disease, However, there were no new findings of osteolysis and no recurrence of CSF leakage in our patient. Since the patient has shown good progress, we plan to continue the same medication. However, it is

unclear whether this condition will remain stable and whether long-term medication is desirable. It is thought that strict follow-up will be necessary in the future.

In conclusion, we performed a transmeatal fistula closure in a patient with GS disease who had CSF leakage due to temporal osteolysis. The fistula was closed by dense filling and compression around the fistula, in the middle ear cavity, and in the external auditory canal. The patient was treated with bisphosphonates and has not shown progression of the disease, but regular and careful follow-up is required.

Acknowledgments: We are grateful to Dr. Tetsuji Uno (Division of Neurosurgery, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University) for assistance with the bone biopsy.

The authors declare no conflict of interest.

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