Cerebrospinal fluid leakage in Gorham-Stout disease due to dura mater involvement after progression of an osteolytic lesion in the thoracic spine

Case report

Eric José Suero Molina, M.D., 1 Thomas Niederstadt, M.D., 2 Vincent Ruland, M.D., 3 Gian Kayser, M.D., 4 Walter Stummer, M.D., 1 Christian Ewelt, M.D., 1 and Jochen Rössler, M.D. 5

Departments of 1Neurosurgery and 1Clinical Radiology, and 1Institute of Neuropathology, University Hospital of Münster; and 2Institute of Pathology and 3Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, University Hospital of Freiburg, Germany

Patients with Gorham-Stout disease (GSD), a rare disease of poorly understood etiology, suffer from progressive osteolysis. Destruction of bone matrix is caused by lymphatic vessels, which can lead to CSF leakage if parts of bony structures adjacent to CSF spaces are involved. So far, fewer than 200 patients have been reported in the literature; only 4 of these patients presented with CSF leakage. The authors report the case of a 30-year-old man with GSD and CSF leakage due to dura mater involvement after progression of an osteolytic lesion in the thoracic spine. Neurosurgical intervention, including dura repair, was needed. Experimental medical therapy with rapamycin was started, leading to disease control for more than 12 months. Progression of GSD can lead to destruction of the meninges, causing CSF leakage. The authors review 4 other cases reported in the literature and discuss therapeutic options.

KEY WORDS • Gorham-Stout disease • CSF leakage • thoracic spine • osteolytic lesion

Vanishing bone disease, disappearing bone disease, idiopathic massive osteolysis, primary lymphangioma, phantom bone disease, and progressive osteolysis are various synonyms used to describe Gorham-Stout disease (GSD). 1-5 Jackson first described GSD in 1838 and 1872, 12,13 in the context of a 12-year-old-boy who presented with complete osteolysis of one humerus over the course of 11 years. In 1955, Gorham and Stout published a review of 24 cases and described progressive idiopathic osteolysis in one or several bones around one focus. 7 Apart from skeletal involvement, soft-tissue manifestation, splenic cysts, or hepatic cysts as well as pleural effusion can be observed; however, these findings occur less frequently than in generalized lymphatic anomaly, another multisystem disorder of lymphatic malformations recently approved by the revised ISSVA (International Society for the Study of Vascular Anomalies) classification. 11

Gorham-Stout disease is a rare disease of poorly understood etiopathophysiology. Aggressive lymphatic and vascular proliferation of unknown origin are believed to be the causes of local destruction and secondary bone resorption. 7 Others have linked bone resorption to increased osteoclast activity, even though an increase in osteoclast numbers could not be shown in analyzed tissues. 16 Once osteolysis ceases to progress, no bone regeneration is observed. 10 The osteolytic defect is filled by marked vascularized fibrous tissue. 19

To date, 4 cases of GSD involving CSF leakage have been published 3,9,17,18 all presenting with lesions involving the petrous and temporal bones or the spinal vertebral bodies (Table 1). In this report we discuss the case of a patient with GSD who presented to our clinic with clinical signs of intracranial hypotension due to CSF leakage as a result of progression of a thoracic vertebral body lesion involving the dura mater with a consecutive CSF fistula.

Case Report

This male patient was diagnosed with GSD at the age...
TABLE 1: Reported cases of GSD and CSF leakage*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age at CSF Leakage, Sex</th>
<th>Symptoms Due to CSF Leakage</th>
<th>Bone Involvement Causing CSF Leakage</th>
<th>Further Manifestations of GSD</th>
<th>Age at 1st Diagnosis of GSD</th>
<th>GSD Treatment</th>
<th>CSF Leakage Treatment</th>
<th>Follow-Up Time After Treatment for CSF Leakage</th>
</tr>
</thead>
<tbody>
<tr>
<td>present case</td>
<td>30 yrs, M</td>
<td>headache</td>
<td>T-11 vertebral body</td>
<td>spinal fusion by transpedicular stabilization; IFN-α2b + pamidronate for 12 mos; lt-sided pleurodesis; rapamycin for 18 mos</td>
<td>13 yrs</td>
<td>neurosurgical dura repair w/ gelatin sponge &amp; TachoSil &amp; fibrin glue; restart of rapamycin</td>
<td>12 mos</td>
<td></td>
</tr>
<tr>
<td>Morimoto et al., 2013</td>
<td>11 yrs, F</td>
<td>headache, nausea, tinnitus</td>
<td>rt petrous apex</td>
<td>not reported</td>
<td>11 yrs</td>
<td>surgical coverage w/ superficial temporal fascia &amp; periosteum flap, sealing w/ fibrin glue; IFN-α2b for 2 mos, propranolol on a continuing basis</td>
<td>4 mos</td>
<td></td>
</tr>
<tr>
<td>Adler et al., 2011</td>
<td>7 yrs, F</td>
<td>worsening postural headaches</td>
<td>L4–5 vertebral bodies</td>
<td>lumbosacral spine, pelvis</td>
<td>1 yr</td>
<td>IFN-α2b + zoledronate for 12 mos</td>
<td>3 CT-guided transforaminal blood patches; CT-guided placement of 0.8 ml of NBCA liquid embolic into the fistula</td>
<td>6 mos; residual symptoms (positional headaches) &amp; intracranial hypotension on MRI</td>
</tr>
<tr>
<td>Cushing et al., 2010</td>
<td>12 yrs, M</td>
<td>headache, nausea, vomiting, tinnitus</td>
<td>rt petrous apex, temporal &amp; parietal bone, malleus</td>
<td>12 yrs</td>
<td>NA</td>
<td>plugging the zygomatic root w/ soft tissue &amp; tissue glue; tympanomastoidectomy, eustachian tube plugging, middle ear &amp; mastoid obliteration w/ abdominal fat graft</td>
<td>6 mos</td>
<td></td>
</tr>
<tr>
<td>Nazarian et al., 1990</td>
<td>3 yrs, 5 mos, F</td>
<td>meningitis w/ lt ear otorrhea</td>
<td>lt ramus of the mandible</td>
<td>temporal &amp; parietal bone</td>
<td>19 mos</td>
<td>2 episodes of meningitis treated w/ antibiotics</td>
<td>after 3rd case of meningitis: bone &amp; fascia overlay to seal the dura of the middle cranial fossa; 3 mos later, 4th meningitis: mastoid packing w/ abdominal fat &amp; temporal fascia</td>
<td>5 yrs; another case of meningitis, since then cephalosporin prophylaxis</td>
</tr>
</tbody>
</table>

* NA = not available; NBCA = N-butyl cyanoacrylate.
of 13 years when an osteolytic lesion in the L-1 vertebral body was biopsied, which revealed the typical morphology of GSD. Multiple splenic lesions confirmed the diagnosis. Over a period of 12 years, the disease was clinically stable. At the age of 26 years, CT imaging demonstrated a compression fracture of the T-12 and L-1 vertebrae after the patient developed chronic dorsalgia without radiculopathy. Furthermore, excessive prevertebral soft-tissue formation at the T7–12 vertebrae with rib head infiltration was observed. The spinal instability of the patient prompted spinal fusion between the T-6 and L-4 vertebrae by transpedicular stabilization through a posterior approach using the Expedium-Titan System (DePuy Spine, Inc.) and Actifuse granules (Curasan) as bone graft substitute. Medical therapy with subcutaneous IFN-α2b and monthly pamidronic acid infusions were initiated. At the age of 27 years, the patient developed a left-sided chylothorax, which was initially drained by pleural puncture but persisted for more than 12 months despite experimental therapy with the mTOR inhibitor rapamycin (Sirolimus). Finally, thoracoscopic pleurodesis was performed when the patient was 28 years old. Rapamycin was stopped 6 months after successful pleurodesis.

At the age of 30 years, the patient presented to our neurosurgery department with cephalalgia. During a 4-week period, his symptoms had slowly progressed. The emergency presentation was due to an acute exacerbation. Recumbent positioning eased his symptoms, suggesting orthostatic headache. Finally, the patient was only able to tolerate his headache by holding his head in a deep position. Cranial MRI revealed brain descent with low-lying cerebellar tonsils 14 mm below the foramen magnum.

With suspected intracranial hypotension, CSF leakage was assumed and the patient was admitted for conservative therapy by means of hydration, bed rest, and analgesics. Control craniocervical MRI performed 7 days after hospitalization demonstrated unaltered low-lying cerebellar tonsils (Fig. 1A). Because of the surgical implanted material, which causes artifacts in radiological imaging, CSF leakage could not be demonstrated by MRI. To diagnose a possible source of CSF leakage, invasive myelography and postmyelography CT were performed. Due to the low-lying cerebellar tonsils, puncture of the subarachnoid space and injection of contrast medium were performed, with anesthesiology and neurosurgery standby to allow for emergency suboccipital craniectomy and C-1 laminectomy in the event of cerebellar tonsillar herniation. An epidural blood patch was attempted after myelography. CT scanning revealed CSF leakage and new, extensive osteolysis at the level of T-11 with intradural air (Fig. 2A and B). Neurosurgical intervention was performed to repair the source of CSF leakage that was located at the T-11 nerve root. Surgically, the spinal canal was approached through a left interlaminar approach at the level of the T-10 and T-11 vertebrae. After removing large quantities of scar tissue, the dura mater and the T-11 nerve root were visualized. Bone tissue appeared highly osteolytic. The site of CSF leakage was detected as pulsatile synchronous CSF leakage from the T-11 nerve root. No further meningeal lesion could be detected during extensive exploration. The nerve root was clipped because it could not be reconstructed, and a gelatin sponge was used to cover osteolytic bone lesions. TachoSil (Takeda) and fibrin glue were used to seal the affected nerve root and involved dura. Ultimately, no residual CSF leakage could be detected during a Valsalva maneuver. Histopathological examination of resected material demonstrated fibrous scar tissue with lymphatic infiltration and dilated lymphatic channels (Fig. 2C and D).

The patient recovered quickly after surgery. Postoperative MRI demonstrated regression of low-lying cerebellar tonsils only 6 mm below the foramen magnum (Fig. 1B). The patient was discharged from the hospital 14 days after surgery. Rapamycin therapy was started again 4 weeks after surgery. The patient remained in good clinical condition without cephalalgia at clinical follow-up 12 months later.

Discussion
The etiopathophysiology of GSD is still poorly understood. In this report we present the case of a 30-year-old man with known GSD with CSF leakage following a dura lesion in the thoracic spine. Gorham-Stout disease usually presents as progressive idiopathic osteolysis of one or several bones around one focus, without respect for joint boundaries. Clinical diagnosis of GSD is challenging, and symptoms are nonspecific. Fractures, often without a history of trauma, lead to pain and dysfunction. Immunohistochemical analysis is needed to discriminate between other important conditions in the differential di-

![Image](A: Sagittal and axial T2-weighted MR images obtained 7 days after admission, showing brain descent with low-lying cerebellar tonsils (double arrow) 14 mm below the foramen magnum, GSD bone lesion (arrowhead), and subdural hygromas (arrow). B: Sagittal and axial T2-weighted MR images obtained 1 year after neurosurgical intervention, showing brain descent with low-lying cerebellar tonsils only 6 mm below the foramen magnum and regression of subdural hygromas.)
Gorham-Stout disease causing dura lesion in the thoracic spine

Fig. 2. Postmyelography CT images showing CSF leakage at the T-11 level (arrow in A) and intradural air and bone osteolysis (arrow in B). Dilated lymphatic channels in fibrous connective tissue with lymphocytic infiltrate (arrow), H & E (C). D2-40–positive staining of lymphatic endothelial cells in the dilated lymphatic channels (D). Original magnification ×20 (C and D).

agnosis, such as osteolytic metastasis, generalized lymphatic anomaly, neurogenic osteolysis, or Paget’s disease. D2-40 expression in lymphatic tissue and CD31 in the endothelial formations are important immunochemical markers for the diagnosis of GSD (Fig. 2D).10 The current treatment aims for symptomatic relief until the etiopathophysiology is known.

Spontaneous intracranial hypotension without history of trauma, lumbar puncture, or epidural injection is characterized by orthostatic headache, low CSF pressure, and diffuse cerebral or spinal pachymeningeal enhancement on MRI.5 In the most cases, a dural tear or spinal meningeal diverticulum is the underlying etiology.20

Patients with GSD focused in the ribs, scapulae, or thoracic vertebrae may develop a chylothorax secondary to infiltration and pathological dilation of lymphatic vessels into the pleural cavity. Others have regarded chylothorax to be related to disruption of the thoracic duct or pleural lymphatic vessels by adjacent osteolysis.2,21 In the presented case, continuous progression of the disease could be observed despite administration of experimental medical therapy. After vertebral body fractures and transpedicular stabilization, the patient was treated with IFN-α2b and bisphosphonates.14 Twelve months after beginning this therapy, he developed chylothorax and rapamycin was administered, but it had no effect for 1 year.9 As a consequence, pleurodesis was performed and rapamycin was stopped 6 months later. CSF leakage developed due to dura mater infiltration when the patient was not on a regimen of any medical therapy. After neurosurgical repair, the patient restarted rapamycin. The patient is currently stable after 12 months of experimental therapy. Taken together, the effect of medical treatment is still not clear and clinical trials to find out which drug is truly effective are urgently needed.

Cases of GSD presenting with CSF leakage are extremely rare. Our literature search revealed 4 other cases (Table 1). In 2 cases a diagnosis of GSD was made when the CSF leakage became symptomatic. Headaches were the main symptom, as was the case in our patient due to reduced intracranial pressure. One child suffered from recurrent meningitis and only at the third episode was CSF leakage identified as an underlying cause. Three cases presented with skeletal lesions of the head, while our case and a recently reported case presented with osteolytic spinal vertebrae as the origin of GSD progressively infiltrating the dura mater. All cases were managed by surgery. Our case and the other most recent case were treated by experimental medical therapy after successful surgery.

Conclusions

Gorham-Stout disease is an unpredictable condition with variable clinical presentation. Disease-associated lymphatic and vascular proliferation may infiltrate surrounding tissue, causing additional damage. If clinical signs of intracranial hypotension are present in GSD, a CSF fistula should be considered in the differential diagnosis. Neurosurgical management by repair of the meningeal defect followed by experimental medical therapy using rapamycin can be successful as shown in our case.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Suero Molina,
References


