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CASE REPORT

Management of Intrathoracic Huge Meningocele in a Case of Neurofibromatosis Type-1, Report of a Case and Review of the Literature

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Background: Meningocele is the extension of the dural sac into the pleural or peritoneal cavity. Thoracic meningoceles mainly occur in neurofibromatosis type-1 (NF-1). It always coincides with kyphosis/scoliosis. Because the initial symptoms are respiratory problems, they are usually misdiagnosed as a massive pleural effusion at first.

Case Presentation: This is a 60-year-old man, a known case of NF-1, who presented with flank pain 8 months before surgery. As an incidental finding in the sonographic evaluation of the urinary system, he was diagnosed and managed as a massive pleural effusion for months until referred to our tertiary center. After further evaluations, a right thoracic huge meningocele was diagnosed. Posterolateral approach for laminectomy, costotransversectomy, ligation of the ectatic sleeves of the spinal nerve roots, cyst resection, dural repair, and spinal fusion was utilized. A pleural and lumbar draining tube was applied for 8 days. The patient recovered completely from his respiratory problems, without any neurological deficit or catastrophic events.

Conclusion: Thoracic meningoceles limit the expansion of the lungs. The diagnosis and management are always challenging. Management of this pathology should include resection of the cyst to decompress the neighboring organs, repair of the dural sac, and reconstruction of the spinal canal. A two-step posterolateral approach was utilized: first, laminectomy and costotransversectomy with ligation of ectatic nerve roots; second, definitive ligation of the fistula, cyst resection, dural repair, and spinal fusion. Although the posterolateral approach typically allows single-stage management, complex anatomy may necessitate a planned second surgery after reassessment with cisternography.

Keywords: neurofibromatosis-1, meningocele, scoliosis, massive pleural effusion

Introduction

Neurofibromatosis-1 (NF-1) is a hereditary genetic disorder of neurocutaneous tissue.[1] Spinal changes include widening of intervertebral foramina, scalloping of vertebral bodies (VB), scoliosis, and dural ectasia, as well as mesenchymal involvement, which can be seen in this disease.[2] It is not clear whether skeletal malformation or the pulsation of the cerebrospinal fluid (CSF) in the dural sac is the primary cause of the dural ectasia.[2,3] Meningocele is defined as the herniation of the meningeal sac through a defect in the spinal column, which can occur posteriorly (as in spina bifida), anteriorly, or laterally into the thoracic or abdominal cavity. Dural ectasia may include the extended sleeves of the nerve roots and/or aberrant stalk of the dural sac.[4] More than 60% of meningoceles are associated with NF-1, and the rest occur spontaneously.[4,5] They usually contain only CSF, but in multiple forms, existing in lateral meningocele syndrome (LMS) in the context of NF-1; neural tissue could herniate in the sac.[5] Solitary meningoceles usually become symptomatic after

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the 5th decade. Their symptoms are mainly due to the compression of neighboring structures and organs. In thoracic meningocele, which is a very rare condition, the patients mainly present with chest tightness and dyspnea.[5,6] That is the reason that these patients are initially misdiagnosed and mismanaged as pleural effusion.[5–7] Many evaluation techniques have been tried for confirmation of the diagnosis and to guide a more targeted surgery. Thoracoscopic evaluation of the cyst and its relations to the spine under direct vision, biochemical confirmation of the CSF content of the cyst, radiologic evaluations, and radionuclide cisternography are among the most popular routes.[8]

Management of meningoceles has involved open surgical approaches before the year 2000, with posterior laminectomy and costotransversectomy, ligation of the ectatic sleeves of the nerve roots, closure of the stalk of the aberrant dural sac, and removal of the meningocele.[8–10] After 2000, because of the introduction of minimal and less invasive interventions, management of meningoceles initially involved cystoperitoneal (CP) shunt, ventriculoperitoneal (VP) shunt, or thoracoscopic ligation; yet, in most cases, initial management failed, and further open surgery was necessitated.[4–7]

In this manuscript, we present a 60-year-old man with NF-1 and scoliosis, who presented with flank pain 8 months ago, with incidental detection of right-sided massive pleural effusion during sonographic evaluation. The initial approach to his symptoms was based on the impression of pleural effusion. After multiple episodes of pleural tapping and analysis for cytology, culture, microbiological, and biochemical evaluations, no definite diagnosis was confirmed. After reviewing chest computed tomography (CT) and magnetic resonance imaging (MRI), a lateral meningocele was diagnosed. We obtained radionuclide cisternography to confirm the connection between the pleural effusion and the dural sac. The management included a two-step open surgical intervention.

Case Presentation

A 60-year-old man with NF-1 was referred to Namazi Hospital for management of massive pleural effusion. He presented with flank pain 8 months before. During the sonographic evaluation of his kidneys, a massive pleural effusion was incidentally detected on the right side. Initial evaluations in the primary and secondary medical centers with physical examination, chest X-ray, and chest CT, revealed abnormal spinal curvature and a huge opaque and hyperdense lesion in the right side of his chest. The primary impression was massive pleural effusion based on NF-1. He went under diagnostic and therapeutic pleural tapping multiple times. The analysis of the fluid for cell count, cytology, microbiology, culture, and biochemical perspectives was negative for any of the usual etiologies of massive pleural effusion (para-neoplastic, hemothorax, transudative, and so on). The symptoms gradually developed with dyspnea, positional headache, and chest pain, which were more severe after each episode of pleural tapping.

In our center, the chest X-ray and CT scan were reviewed. Lower thoracic scoliosis at the T7-T10 level, with the apex at the T8-T9 level and convexity to the right side, was confirmed (Figure 1). In the chest CT-scan, scalloping of the posterior wall of T7-T10 vertebral bodies, widening of T8-T10 intervertebral foramina on the right side, and expansion of the spinal canal at the T7-T10 level were also documented (Figure 2).

The patient went under further imaging evaluations with chest sonography and thoracic MRI. In the T2-weighted sequence of his thoracic MRI (Figure 3), high signal intensity of the content of the cyst, in continuation with the CSF of the dural sac, appeared at the T7-T10 level. After sessions of an interdisciplinary conference and reviewing all the gathered data from the evaluations, a huge thoracic lateral meningocele in the right pleural space was hypothesized. In order to confirm the diagnosis of meningocele, as ß-2-Transferrin was not available, we chose to perform radionuclide cisternography in order to prove that the content of the cyst is CSF (Figure 4). The single-photon emission computed tomography (SPECT) also confirmed that this connection is through the right T8-T10 intervertebral foramina. After reviewing the literature on the subject in the spine surgery team of the neurosurgery group, the posterolateral approach was taken.

Operative Technique

On the operation day, after general anesthesia, the patient was intubated with a double-lumen orotracheal tube. Intraoperative neuromonitoring (IONM) was applied for assessment of somatosensory and motor evoked potentials (SSEP and MEP) prior to positioning till the end of the procedure and repositioning. In standard prone position, after midline incision and soft tissue dissection, hemilaminectomy and costotransversectomy of T8-T10 were performed on the right side. The ectatic sleeves of the nerve roots were ligated with 2–0 silk string.

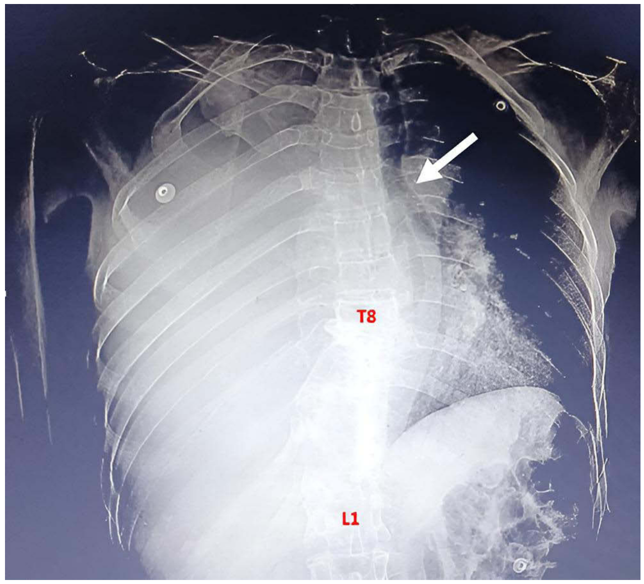

Figure 1 The antero-posterior chest X-ray shows lower thoracic scoliosis at the T7-T10 level, with the apex at the T8-T9 level and convexity to the right side, right-sided chest opacity (unilateral white lung), and deviation of bronchi to the left side (white arrow).

After 48 hours, radionuclide cisternography and SPECT were repeated (Figure 5). It revealed the persistence of the cyst at the same level with a marked reduction in volume. It also revealed the low-pressure connection between the dural sac and the cyst at the T9-T10 level, where the nerve roots were ligated. After obtaining SPECT, the exact location of the fistula was located between and just ventral to the right T9-T10 nerve roots. We concluded that after ligation of the accused nerve roots, the low-pressure (or collapsed) fistula became prominent. Thus, we decided to perform the second surgery in order to ligate the fistula.

At the second surgery, after expansion of the laminectomy and retraction of the sacrificed nerve roots (right T8-T10) medially, the stalk of the cyst was observed in the ventrolateral portion of the dural sac and followed laterally to expose the margins of the meningocele in the pleural space (Figure 6a). Lateral durotomy was done at this point to observe the spinal cord under direct vision. Two strings were passed around the stalk with a 2 cm interval and knotted tightly (Figure 6b). The stalk was cut from the interval between the two knots, and the proximal orifice was primarily sutured with 3–0 Prolene string. The meningocele margins were followed, dissected from the two pleural membranes, and then removed without major bleeding as much as possible. The lateral durotomy site was then primarily sutured with 5–0 Prolene sutures. A vascularized musculofascial flap of the paraspinal muscles was then mobilized and sutured on the lateral part of the dural sac to support the duratomy site and the ligated stalk of the cyst in the spinal canal. Bilateral T4, T5, T12, and L1 pedicular screws were inserted and connected with contour rods, without further unnecessary effort to correct the slight (<30°) curvature of the thoracic scoliosis. The surgical site was tightly closed layer by layer. IONM was without any significant change during the surgery, and total blood loss was <1500 mL. After repositioning, the right pleural and lumbar draining tubes were applied. The chest tube was kept in place for 10 days in place, until the draining fluid was measured <30 mL per shift (8 hours). The head of the bed was adjusted to less than 10° elevated, and a lumbar draining tube was planned for drainage of 10–30 mL every 8 hours, with close observation of overdrainage symptoms, for 8 days. For anticoagulation prophylaxis, mechanical compression was applied from the time of general anesthesia, and enoxaparin was ordered on the 3rd day after surgery. The early postoperative course was uneventful.

At the 14th day of postoperative course, radionuclide cisternography was performed, and no major leakage of CSF was noticed (Figure 7). Both draining tubes were removed without complication. No neurological sign or symptom was detected in the first 10 days of the postoperative period.

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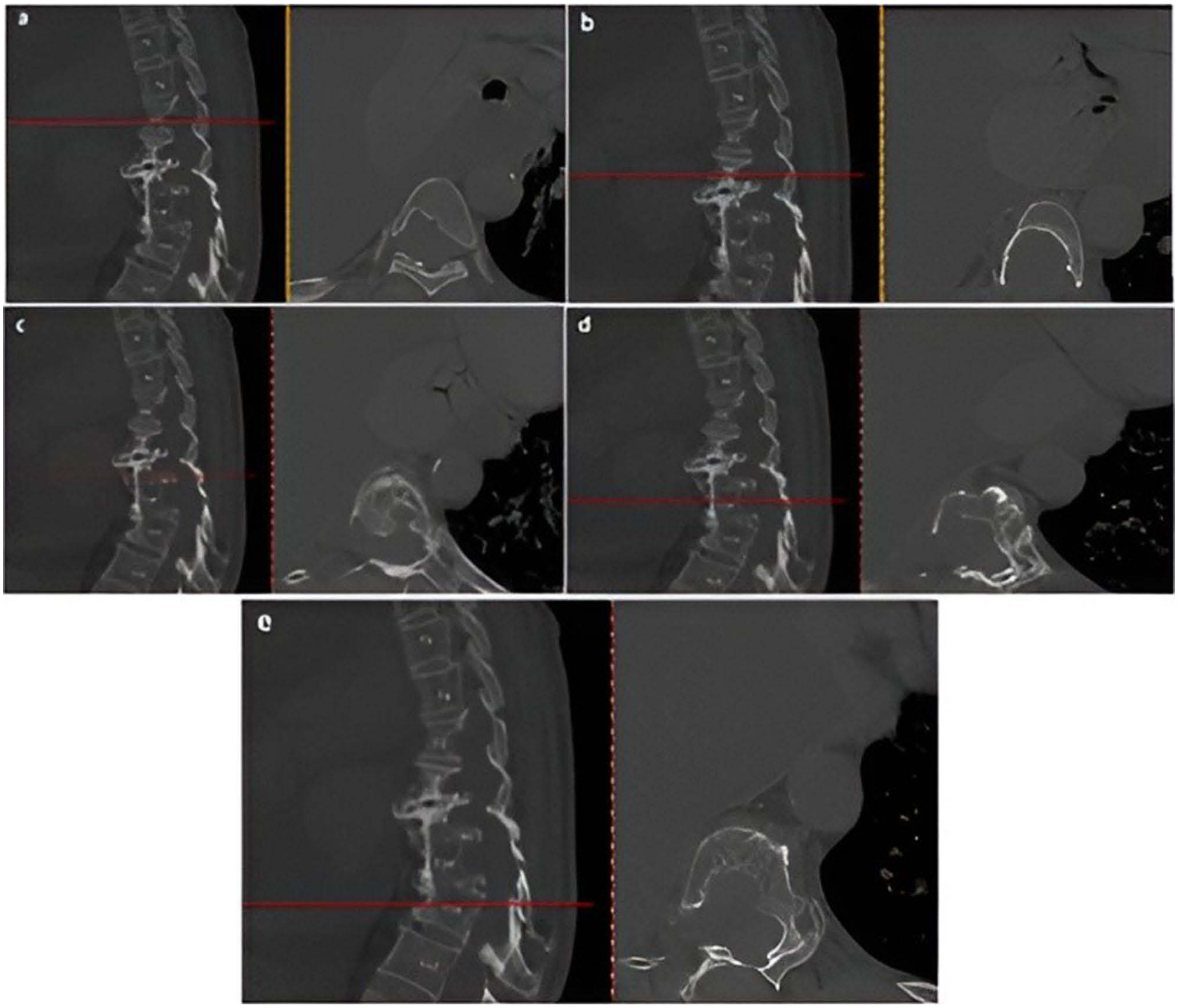

Figure 2 Cross-view of the axial-sagittal chest CT-scan. The scalloping of the posterior wall of the vertebral bodies, widening of the spinal canal, and right intervertebral foramina of T7-T10 (**a**-**e**) level is indicated.

Discussion

Lateral meningoceles are far less common than the dorsal-midline types.[4] The thoracic meningoceles are also less common than the lumbopelvic variants.[4,5] It has once been reported in the foramen magnum, in a patient with NF-1.[11] The pathophysiology of the dorsal type is the dysraphism of the spinal column, while the lateral types are always associated with malformations of the vertebral elements, such as scalloping of the vertebral body, scoliosis, and widening of the intervertebral foramina.[4–7] Lateral meningoceles have been reported independent from NF. It is also seen in the context of COVID-19.[12] Before 2000, according to some hypotheses, meningoceles in the context of NF were considered as a cystic transformation of a dumbbell-shape nervesheath tumor.[13–15] The pressure gradient at the apex of the scoliosis, between the intra- and extradural spaces, is the main pathophysiologic process.[4–7,10,16] For further explanations, dysplastic mesenchyme, including dura mater and bony elements, causes a series of events leading to the formation of meningoceles.[9,10,16,17] The scoliosis might be the initiating event in these consequences. At the convexity of the apex, the pulsation of the CSF, beside the negative pressure of the pleural cavity, puts a pulsatile, high gradient pressure on the dysplastic bony elements at the intervertebral foramina.[17,18] It causes gradual widening of the foramina, scalloping of the vertebral body, and the sprouting of the dura mater out of the column.[19–22]

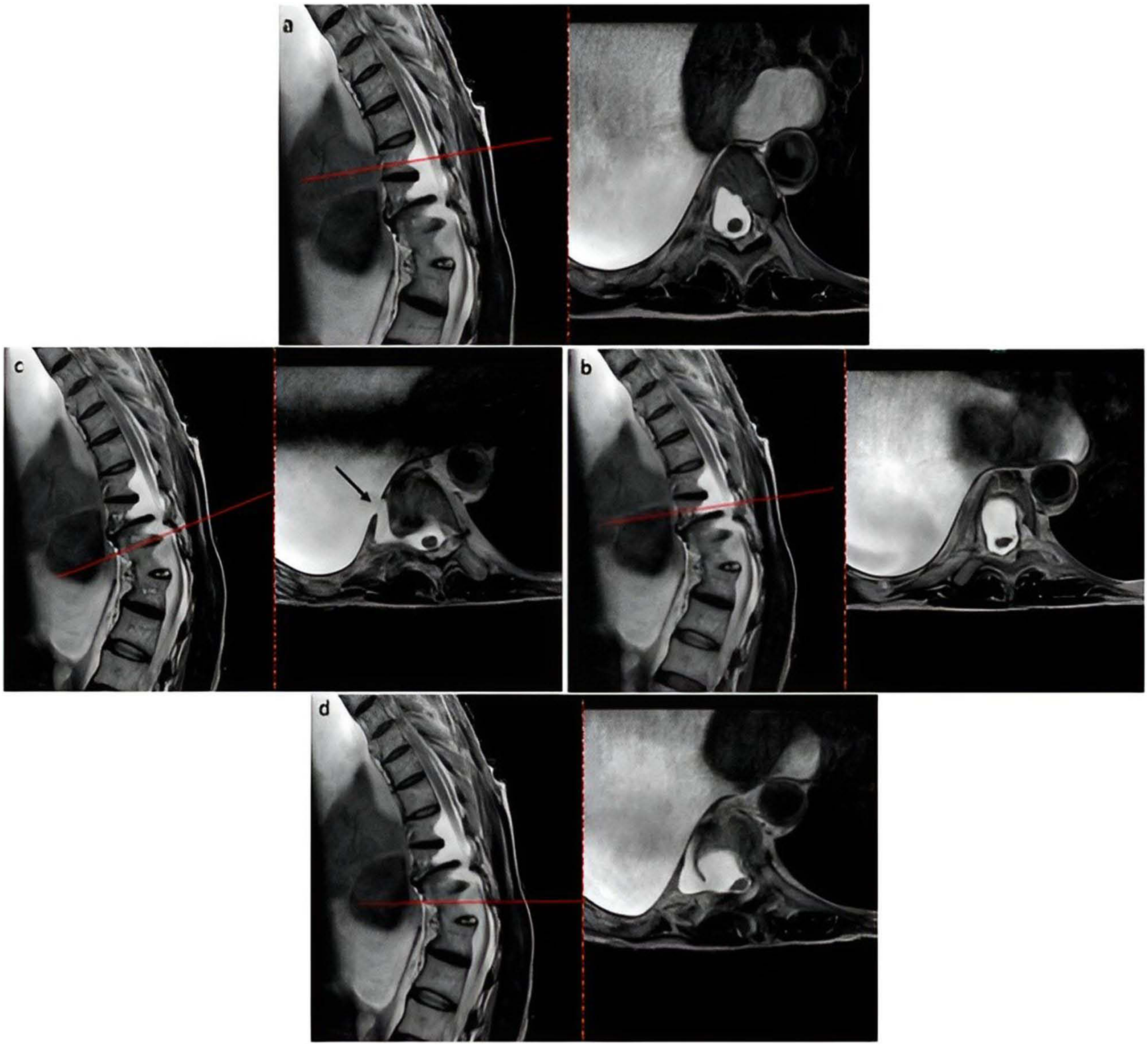

Figure 3 Cross-view of the axial-sagittal T-2 weighted sequence of chest MRI. High signal intensity of the content of the cyst was obviously present at the T7-T10 level (**a**-**d**), in continuation with the CSF of the dural sac (black arrow in "c").

As the expansion of the cyst in spontaneous lateral thoracic meningocele is gradual, the adaptation of the CSF dynamics prevents the development of any signs and symptoms of intracranial hypotension; in contrast to iatrogenic meningoceles.[19–21,23] Yet, intracranial hypotension has been reported as the presenting symptom of NF-associated thoracic meningocele.[24,25] Furthermore, if the herniation of the spinal cord and neural elements does not occur, which usually does not, a neurological deficit is very rare.[26] Although in most of such cases, respiratory problems are the presenting symptoms, they might be found incidentally due to remodeling of the lungs.[17,18,20,23] In LMS and iatrogenic meningoceles, neurologic deficit and intracranial hypotension symptoms are the main presenting problems.[5,6,19,22] In our presented case, although the presentation was due to the flank pain (irrelevant to the meningocele), the repeated pleural taps of the incidentally found meningocele led to the development of mild signs and symptoms of intracranial hypotension when referred to the tertiary center.

In cases of meningocele, there are many diagnostic challenges. The initial approaches to these patients have always been based on their respiratory symptoms.[4] In some studies, final diagnosis was achieved by reviewing radiologic evaluations by a team of clinicians and radiologists,[8] while Chen. et al mentioned the role of the evaluation of ß-

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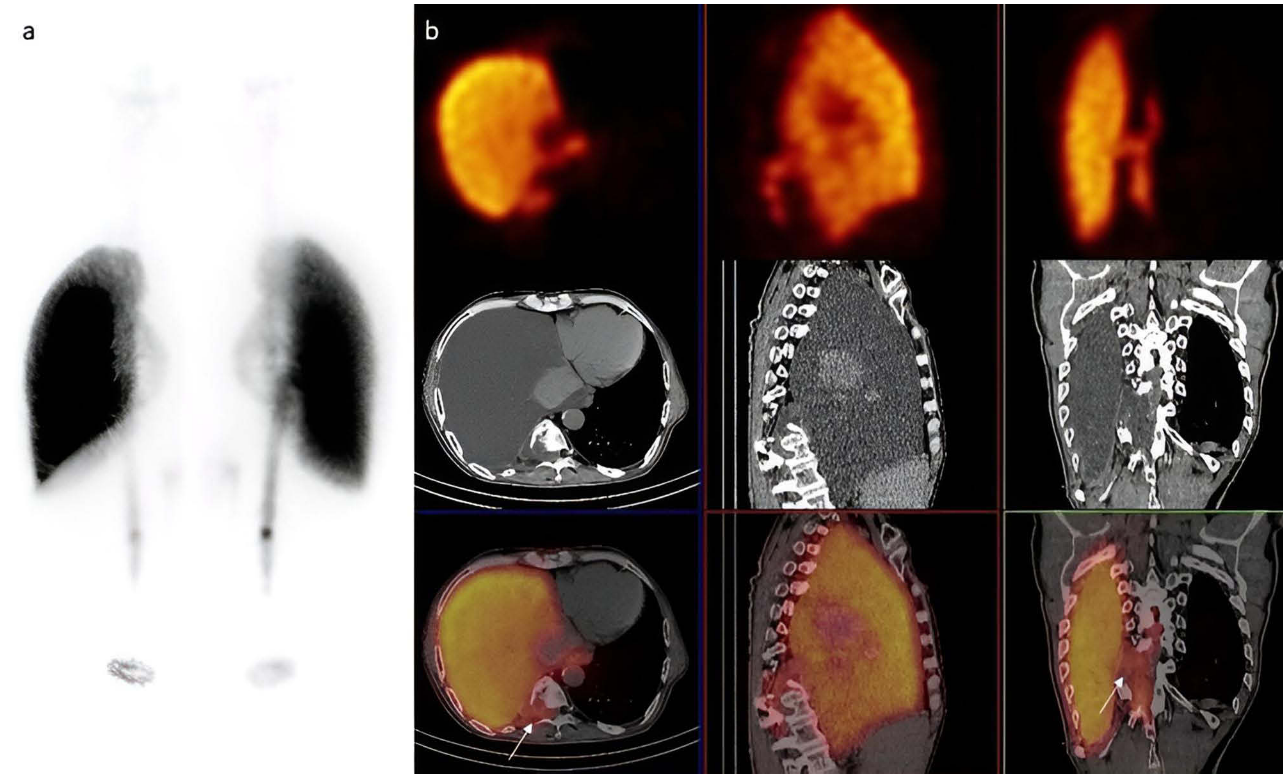

Figure 4 Pre-operative radionuclide cisternography: Anterior and posterior whole-body images (**a**) obtained 2 hours after injection of 10 mCi 99mTc-DTPA via lumbar puncture, revealed the radiotracer accumulation in the spinal column till a mid-thoracic level, where a connection was seen through the right pleural space, which abnormally contained the radiotracer. The 3-dimensional SPECT (upper row), low-dose CT (middle row), and fused SPECT/low-dose CT (lower row) (**b**) localized the level of abnormal CSF connection between the spinal and right pleural space at the T8-T10 right intervertebral foramina (white arrows). The images also showed ectasia of the spinal column at multiple adjacent levels; however, there is a little ascent of radiotracer above the level of leakage, evaluating upper parts less reliable.

2-Transferrin in the tapped fluid in diagnosis.[7] In some reports, the visualization of the stalk of the cyst under direct vision with a thoracoscope has been the confirmation method.[27,28] Another diagnostic challenge is ruling out subarachnoid-pleural fistula, which is always a consequence of trauma, surgery, or an underlying mass.[19] Lateral meningocele syndrome is another differential diagnosis that occurs in pediatric patients with NF-1 who usually present with neurological symptoms. They have bilateral and multiple lateral meningoceles in the thoracic and abdominal cavity, containing CSF and neural tissue, besides craniofacial malformations.[5] Nuclear cisternography has been used in the literature to confirm the leakage of the CSF out of the dural sac.[8] We performed radionuclide cisternography in order to confirm the CSF outflow from the dural sac into the cyst, and SPECT to determine the exact location of the leakage. It provided us with more detailed information on the leakage and more accurate planning for surgery.

In the published literature before 2000 on this subject, initial management was surgical removal of the meningocele sac through thoracotomy[16] or posterolateral approach,[9,16] including laminectomy and costotransversectomy. Comparing surgical approaches, open techniques (posterolateral approach vs thoracotomy) offer the advantage of direct visualization of neural structures and definitive repair but may require more extensive dissection. Minimally invasive options such as cystoperitoneal shunting or thoracoscopic ligation are less invasive initially; however, as shown in Table 1, many such cases ultimately require conversion to open surgery due to failure or recurrence. The choice of approach should be individualized based on cyst size, anatomy, presence of neural tissue in the sac, and associated spinal deformity. For example, one study stated that for small lesions, laminectomy and closure of the stalk of the cyst is enough, while thoracotomy is mandatory to manage the large ones.[29] In Chen's study in 2024, all reported cases of meningocele after 2000 were reviewed.[7] In the aspect of management, we can conclude that before 2014, open surgical approaches (mainly including posterolateral approach for laminectomy and costotransversectomy) for cyst resection and primary dural repair were the chosen attitude.[9,16] Although shunting was reported as a successful management in a study in 1991,[30] from 2014, cystoperitoneal (CP), lumboperitoneal (LP), and

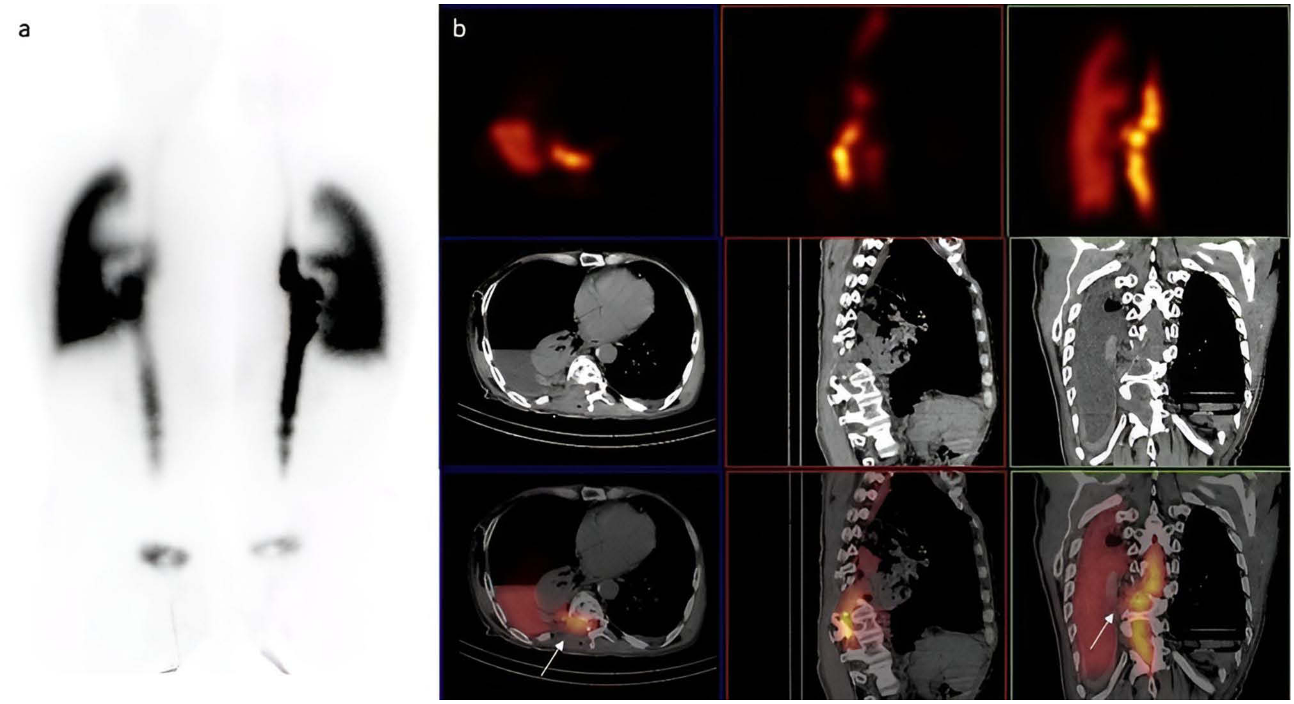

Figure 5 First post-operative radionuclide cisternography: Anterior and posterior whole-body images (**a**) obtained 2 hours after injection of 10 mCi 99mTc-DTPA via lumbar puncture depicted less CSF-containing fluid accumulation in the right pleural space as compared to the pre-operative study, with evidence of more upward CSF flow above the level of abnormal spinal-pleural connection. The 3-dimensional SPECT (upper row), low-dose CT (middle row), and fused SPECT/low-dose CT (lower row) (**b**) revealed the presence of a prior connection level at T9-T10 right intervertebral foramen with evidence of a smaller opening to the right pleural space (white arrows). Due to the insertion of a chest tube in the right pleural space, a significant pneumothorax is also noted.

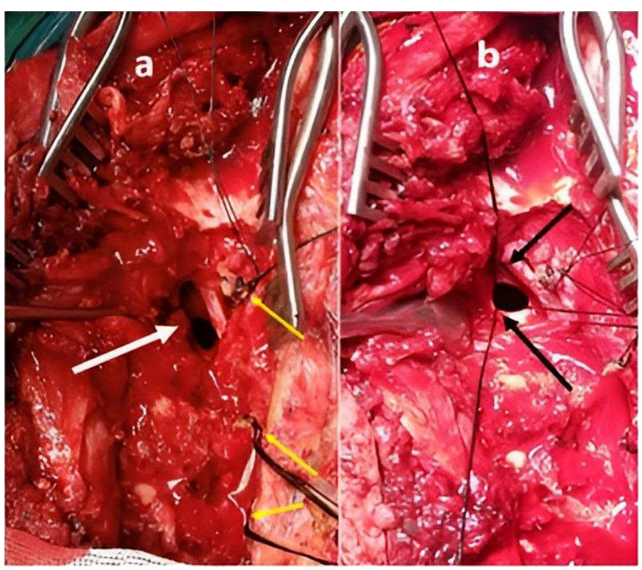

Figure 6 Intraoperative photograph of the second surgery. The sacrificed nerve roots (T8-T10) in the first surgery were retracted medially (yellow arrows in (**a**)) to expose the orifice of the main fistula (white arrow in (**a**)). Two strings (black arrows in (**b**)) were passed around the orifice of the fistula to ligate and cut it.

ventriculoperitoneal (VP) shunts have been utilized as the primary less invasive intervention.[6,27,31,32] The reason could be the impression that hydrodynamic abnormality in the CSF circulation is the main cause of meningocele.[26,33] The majority of such cases lead to second or third surgery (Table 1). We concluded that the open surgical approach for resection of the cyst and

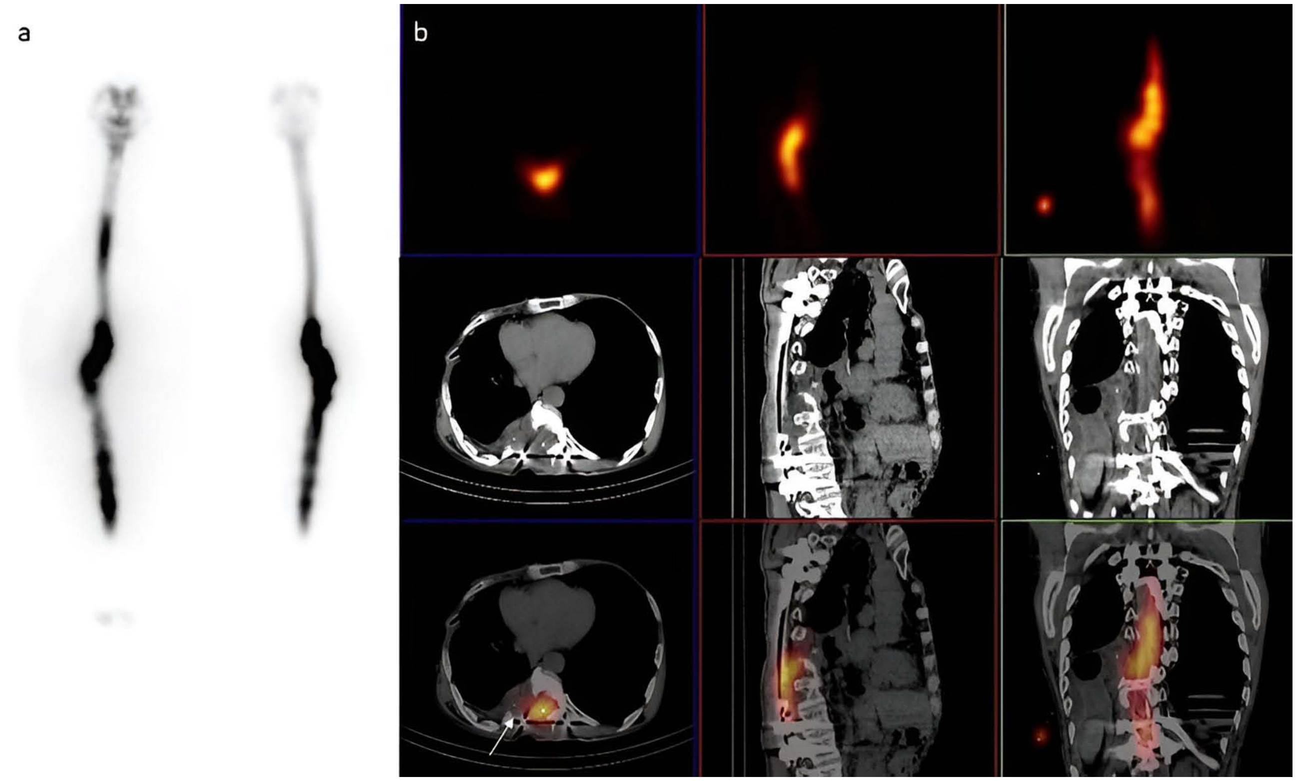

Figure 7 Last post-operative radionuclide cisternography: Two weeks after the last operation, anterior and posterior whole-body images (**a**) obtained 2 hours after injection of 10 mCi 99mTc-DTPA via lumbar puncture, showed normal flow of radiotracer through the spinal column to the basal cisterns with no evidence of abnormal retention or extension of activity outside the spinal column. There is still mild abnormal alignment of the spinal column. The 3-dimensional SPECT (upper row), low-dose CT (middle row), and fused SPECT/low-dose CT (lower row) (**b**) also revealed that the CSF activity is confined to the spinal space at the level of T9-T10 vertebrae (white arrows).

reconstruction of the dural sac is the mainstay of managing meningocele. The important parts in this scenario, based on the similar reports in the literature, are:

- Direct visualization of neural structures (especially the spinal cord),
- Safety of the scarification of thoracic nerve roots with ectatic dural sleeves,
- Support the repaired site of the dural sac with vascularized soft tissue with or without biocompatible glue,
- Reconstruction of the spinal column with fusion to prevent the application of negative pressure to the spinal column from outside,
- Mechanical pleurodesis,
- Sufficient drainage of pleural fluid and CSF in the postoperative course for at least 3–5 days (19–40).

In our study, as the report of the first radionuclide cisternography mentioned, the ectatic nerve roots of T8-T9 on the right side were the origin of the sac; we decided to ligate and sacrifice them through unilateral dissection and laminectomy. In the second scan, the aberrant stalk of the cyst became prominent. We assumed that this was the low-pressure connection of the cyst to the dural sac, which became high-pressure after ligating the other two connections. As the wide laminectomy and facetectomy indicated in the second operation to access the stalk, we performed spinal fusion.

Conclusion

Changes in the hydrodynamic pressure of the spinal column and the dural sac are the main cause of meningocele formation. Abnormal bone quality in NF-1 patients and appearing at the convex part of the scoliosis, besides the negative pressure of the pleural space, are milestones in the formation of meningoceles. Therefore, management of these cases must include not only the decompression of the lungs, but reconstruction of the spinal column and the dural sac to reverse

Table 1 The Review of the Reports of the Spinal Meningoceles Since 2000

Author	Year	Age/ Gender	Pathology	First Operation	Second Operation	3rd Operation	Follow-Up
Our study	2025	60-M	Solitary meningocele	Laminectomy + costotransversectomy + ligation of the ectatic sleeves of the nerve roots	Ligation of the stalk of the meningocele + excision of the meningocele with dura repair + spinal fusion	-	No CSF aberrant flow and leakage, Normal neurological status
[19]	2024	54-F	Solitary meningocele	Thoracotomy for cyst marsupialization and decompression + dural patch and fibrin glue	Laminectomy, pediculectomy, and ligation of the stalk of the cyst with a titanium aneurysm clips	-	Complete recovery
[34]	2024	51-F	Solitary meningocele	Thoracoscopic resection and repair	-	-	Complete recovery
[26]	2024	50-M	Bilateral thoracic meningocele	CP shunt	-	-	Good recovery
[31]	2022	44-M	LTM	Decompressive laminectomy and excision of the meningocele with dura repair.	-	-	Died of pneumonia
[33]	2021	56-F	Solitary meningocele	CP shunt (2 times)	T2–3 costotransversectomy, intradural closure of the meningocele opening with spinal dura and autologous fascia lata + Trapezius muscle regional flap	VATS + latissimus dorsi flap and synthetic materials + Mechanical pleurodesis	
[27]	2021	41-F	Two meningocele	EVD + thoracoscopic exploration	Thoracotomy for resection and repair + latismus dorsi flap	VATS	Complete recovery
[35]	2020	49-M	Solitary meningocele	Thoracotomy for cyst resection and repair + mesh application	-	-	Complete recovery
[32]	2019	59-F	Solitary meningocele, Syrinx, tonsillar herniation	LP shunt	VP shunt	-	No neurological recovery, complete resolution of syrinx and tonsillar herniation
[36]	2017	43-F	Solitary meningocele	CP shunt	Posterolateral thoracotomy with resection of the meningocele and reconstruction of the dural sac	Repair with polypropylene mesh and titanium mesh	Complete recovery
[28]	2017	53-F	Solitary meningocele	Laminectomy and costotransversectomy + scoliosis correction	-	-	Recurrence of meningocele, died of metastatic breast cancer.
[6]	2015	52-F	Double meningocele	CP shunt	Posterolateral thoracotomy for cyst resection and primary repair	-	Complete recovery

(*Continued*)

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Table 1 (Continued).

Author	Year	Age/ Gender	Pathology	First Operation	Second Operation	3rd Operation	Follow-Up
[37]	2014	48-F	Solitary meningocele	Thoracoscopic CP shunt	Intrathoracic meningocele plication under thoracoscopic guidance	-	Complete recovery
[38]	2014	43-F	Solitary meningocele	Thoracotomy for cyst resection and repair + spinal fusion with lateral strut graft using fibula bone graft	-	-	Complete recovery
[39]	2014	45-F	Solitary meningocele	Thoracotomy for cyst resection and primary dural repair + fibrin glue	-	-	Complete recovery
[40]	2011	46-M	Solitary meningocele	Thoracotomy for cyst resection and primary dural repair	-	-	Complete recovery
[41]	2011	48-M	Solitary meningocele	Thoracotomy for cyst resection and primary dural repair	Spinal cord decompression and fusion	-	Complete recovery
[42]	2011	66-F	Solitary meningocele	CP shunt	Endovascular and open surgical approaches to resolve massive hemothorax and bleeding	Thoracotomy for cyst resection and repair (failed)	Died due to respiratory failure
[43]	2011	47-F	Multiple meningocele	CP shunt	-	-	Complete recovery
[44]	2008	60-F	Solitary meningocele	CP shunt	-	-	Complete recovery
[45]	2003	59-M	Solitary meningocele	Thoracotomy for cyst resection and primary dural repair	-	-	Complete recovery
[46]	2003	59-M	Solitary meningocele + severe kyphoscoliosis	Posterolateral laminectomy and costotransversectomy for cyst resection and repair	Posterior fusion from C3 to L2	-	Construct failure
[47]	2002	67-F	Solitary meningocele	Posterolateral laminectomy and costotransversectomy for cyst resection and repair	Nerve root ligation and repair of dural defect	-	Complete recovery
[48]	2002	16-M	Solitary meningocele + severe kyphoscoliosis	Thoracotomy for cyst resection and primary dural repair	Spinal fusion	-	Partial recovery

Abbreviations: CP, cistoperitoneal; CSF, cerebrospinal fluid; EVD, external ventricular device; LP, lumboperitoneal; LTM, lateral thoracic meningocele; VATS, Video-assisted thoracoscopic surgery; VP, ventriculoperitoneal.

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the effect of the negative pressure of the chest on these structures. Resection of the cyst should also be performed whenever direct visualization of the spinal cord is available. With the thoracotomy procedure, the decompression of the lung and safe resection of the cyst are available, but spinal fusion necessitates a second posterior/posterolateral approach. Thus, we chose the posterolateral approach to perform all the surgical goals in one approach and reduce risks and complications.

Abbreviation

NF-1, Neurofibromatosis type-1; VB, Vertebral bodies; CSF, Cerebrospinal fluid; LMS, Lateral meningocele syndrome; CP, Cystoperitoneal; VP, Ventriculoperitoneal; MRI, Magnetic resonance imaging; CT, Computed tomography; SPECT, Single-photon emission computed tomography; IONM, Intraoperative neuromonitoring; SSEP, Somatosensory and evoked potentials; MEP, Motor evoked potentials.

Data Sharing Statement

The data used to support the findings of this study are included within the article.

Ethical Approval and Patient Consent Statement

Institutional approval from the Ethics Committee of Shiraz University of Medical Sciences (ethics code number IR. SUMS.MED.REC.1404.026) was obtained for the publication of this case report and any accompanying images. Informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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