A 34-year-old Female with Neurofibromatosis Type 1 Presenting with Upper Thoracic Intradural Extramedullary Dumbbell Neurofibroma Extending and Obliterating the Right Posterior Mediastinum: A Case Report

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Abstract

Introduction. Neurofibromatosis type 1 (NF1) is an autosomal dominantly inherited condition seen in one of 4000 live births, predisposing to peripheral and central neurofibromas. Spinal tumors are seen in 40% of cases with NF1 and only 2% will develop symptoms, and among those who develop symptoms where 33% showed intradural extramedullary location. Thoracic spinal dumbbell neurofibroma is even rarer, and cases that extend to obliterate the posterior mediastinum even more so, with the case presented being the largest in size documented to date.

Case. A 34-year-old female presented since childhood clinical findings consistent with Neurofibromatosis Type I: generalized cafe-au-lait macules, axillary freckling, cutaneous neurofibromas, two iris Lisch nodules identified via slit lamp examination, and anterolateral bowing of the right tibia, and no known parental history of Neurofibromatosis Type I. Prior to admission, the patient presented with progressive loss of motor strength of the lower extremities, and progressive dyspnea. Work-up revealed a Thoracic Intradural Extramedullary Neurofibroma extending to the Right Posterior Mediastinum measuring 15.3 cm x 12.9 cm x 9.7 cm in the thoracic cavity compressing the right lung and bronchus. An extensive two stage surgery was contemplated involving an initial resection of the Intradural mass, with spine instrumentation for support, and subsequent resection of the mediastinal extension. However, complications from the compressing tumor: complete cord transection syndrome causing spinal autonomic dysfunction, lung and airway compromise causing prolonged intubation and difficulty in weaning from mechanical ventilatory support, extensive thrombus formation in the right jugular vein, and nosocomial infections all created compounding difficulties for the surgical technique and anesthetic plan.

Cornerstone management for dumbbell spinal neurofibromas involves their total removal. The best results are obtained in patients showing minimal neurological deficits during the preoperative period. However, little improvement may be expected from patients who develop complete transection syndrome during the postoperative period. Concurrent medical management to prepare the patients are equally important. The multi-subspecialty approach required in managing these cases entails a good balance between the disability before the surgery, anticipated outcomes, and quality of life of the patients.

Keywords: Neurofibromatosis Type 1, Dumbbell Neurofibroma

Introduction

Neurofibromatosis Type 1 (NF1) is a genetic disorder characterized by a predisposition of individuals to various forms of neoplasms, including neurofibromas. Spinal dumbbell neurofibroma is a rare form of spinal tumor that originates from an intraspinal component and extends through the intervertebral foramen to form the extraspinal component. Spinal involvement among

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patients with NF1 vary ranging from 40% up to 60% of cases. Dumbbell neurofibromas account to 10% of spinal tumors, and only 2% become symptomatic. The commonly affected sites are the cervical and thoracic, with the lumbar region being less frequently involved. [5,7]

Surgical intervention is required when there is neurological deficit, intractable pain, nerve root compression, or progressive tumor growth. The goal of surgery is to remove the intraspinal component first for decompression and then followed by the resection of the extraspinal component. Postoperative outcomes are closely correlated with the burden of preoperative neurological impairment. Those with severe deficits are expected to have poor surgical outcomes. Risk of recurrence is high among patients with NF1 due to the intrinsic infiltrative and multifocal nature of neurofibromas.[12]

We present a 34-year-old female with an extensive thoracic dumbbell neurofibroma, highlighting the numerous complications encountered and the challenges faced in its management.

Case

A 34-year-old female was admitted due to progressive dyspnea. The patient was born with a right limb defect, described as anterolateral bowing of the lower leg. Her lower extremities became atrophic as she grew up but was still able to ambulate unassisted with a limp. She was also noted to have generalized brownish macules. The number of the brownish macules increased, particularly over her trunk, as she grew older.

Four years prior, routine annual health check-up incidentally revealed a suspicious density, possibly a mass, in the right upper to middle lung field on chest radiograph. She was advised to secure further imaging studies but these were not done.

Over the ensuing years the patient experienced progressive tingling sensations in the bilateral lower legs, associated with weakness, starting approximately three years prior. Her bilateral lower extremity weakness gradually worsened rendering her bedridden by one year prior to admission. She had also lost pain and temperature sensations up to the inguinal area.

The patient then developed bouts of non-productive cough one month prior, associated with dyspnea that was relieved by lying on her right side. Her dyspnea gradually worsened, occurring even at rest, prompting her to seek consultation at a hospital. Initial management with nebulization and oxygen supplementation did not provide relief hence, she was referred to a higher institution for further work-up and evaluation.

The patient has no known comorbid conditions, and no history of previous surgical procedures nor hospitalizations. She is the ninth of ten siblings, and no other immediate family members presented clinical features like her. She had been unemployed 3 years prior to admission because of her current illness, and has never smoked nor drank any alcoholic beverages. The patient is Gravida 1 Para 1 (1001) and gave birth to a daughter at 24 years old via normal spontaneous vaginal delivery, with her partner who died of an unrecalled malignancy.

The patient was received at the emergency room with stable vital signs, albeit dyspneic, with an oxygen saturation of 96% on room air. She notably presented with chest lag on the right during respiration, decreased breath sounds on auscultation of the right hemithorax with decreased tactile and vocal fremitus, absence of spontaneous motor movement of the bilateral lower extremities; chest point-of-care ultrasound revealed pleural effusion on the right. She was then managed as a case of Massive Parapneumonic Pleural Effusion, right but malignancy could not be ruled out. Empiric antibiotics (ceftriaxone and azithromycin) were initiated

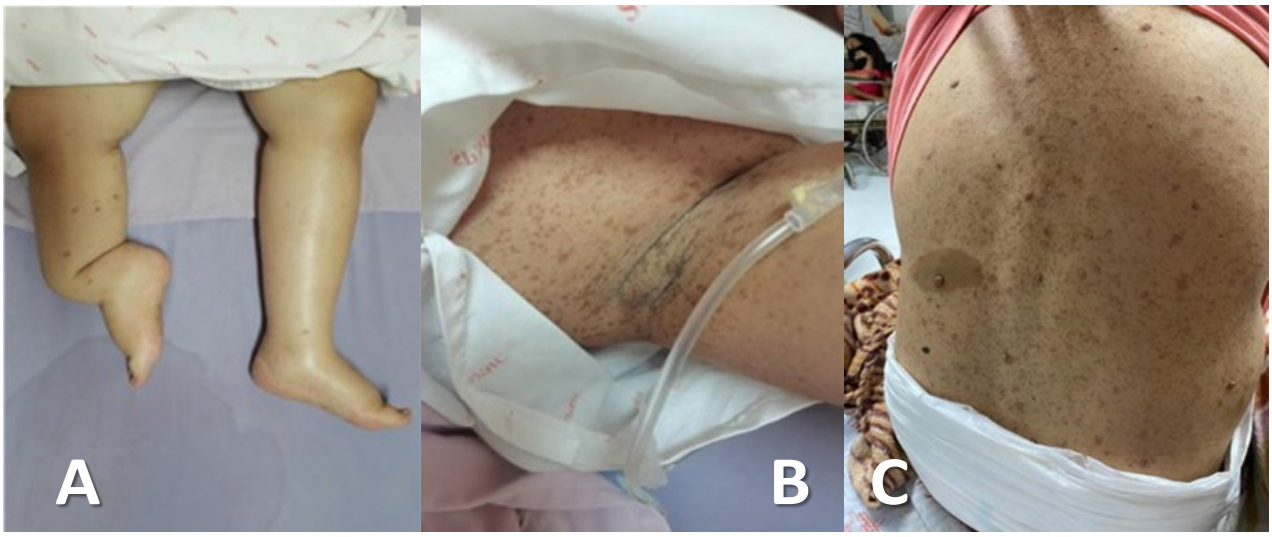

Figure 1. Showing manifestations of (A) bowing of left tibia with pseudoarthrosis, (B) axillary freckling, and (C) café au lait spots and cutaneous neurofibroma.

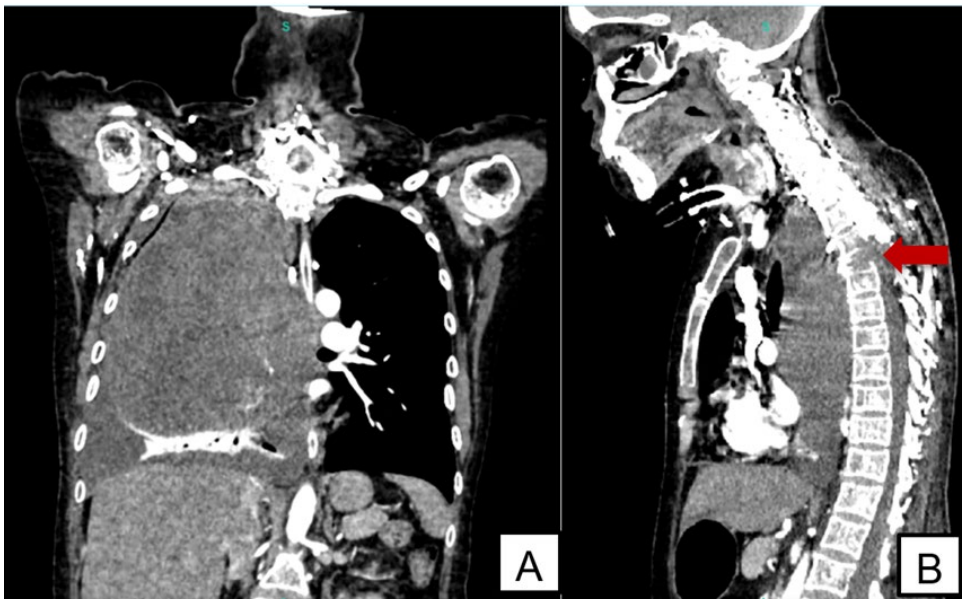

Figure 2. CT scan with Contrast showing (A) coronal section and (B) sagittal section of the mass occupying the right thoracic cavity originating from the T3 - T4 level causing pathologic fracture in T4 vertebra (red arrow) then extending and obliterating the posterior mediastinum, causing displacement of the right main bronchus

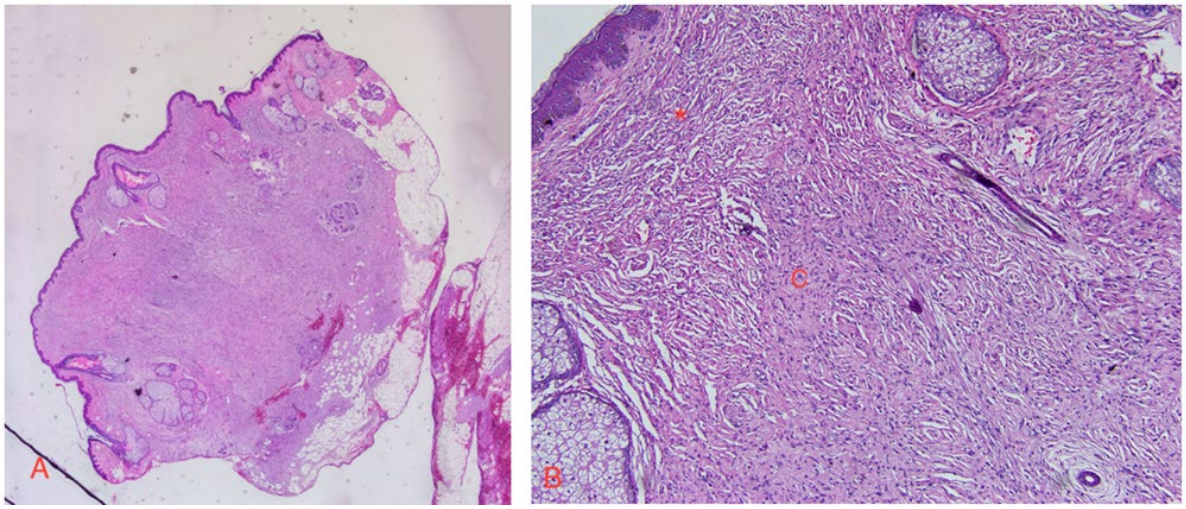

Figure 3. Skin punch biopsy of nodule from forehead. (A) Scanning power at 40x total magnification of neurofibroma. (B) Low power at 100x total magnification showing basketweave pattern of the stratum corneum, atrophic epidermis with basal layer hyperpigmentation, hyperproliferation of spindle cells (indicated by asterisk), and interspersed collagen bundles (indicated by C), suggesting a neurofibroma.

and referred to Interventional Radiology for ultrasound-guided thoracentesis. Approximately 500 mL of serosanguinous fluid was drained, with a cell count of 800/uL with lymphocytic predominance, and a red blood cell count of more than 10,000/uL suggesting either infectious possibly tuberculous or a neoplastic process.

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On the fifth hospital day, she became severely dyspneic and hypotensive. She was subsequently intubated and started on double inotropic support (norepinephrine and

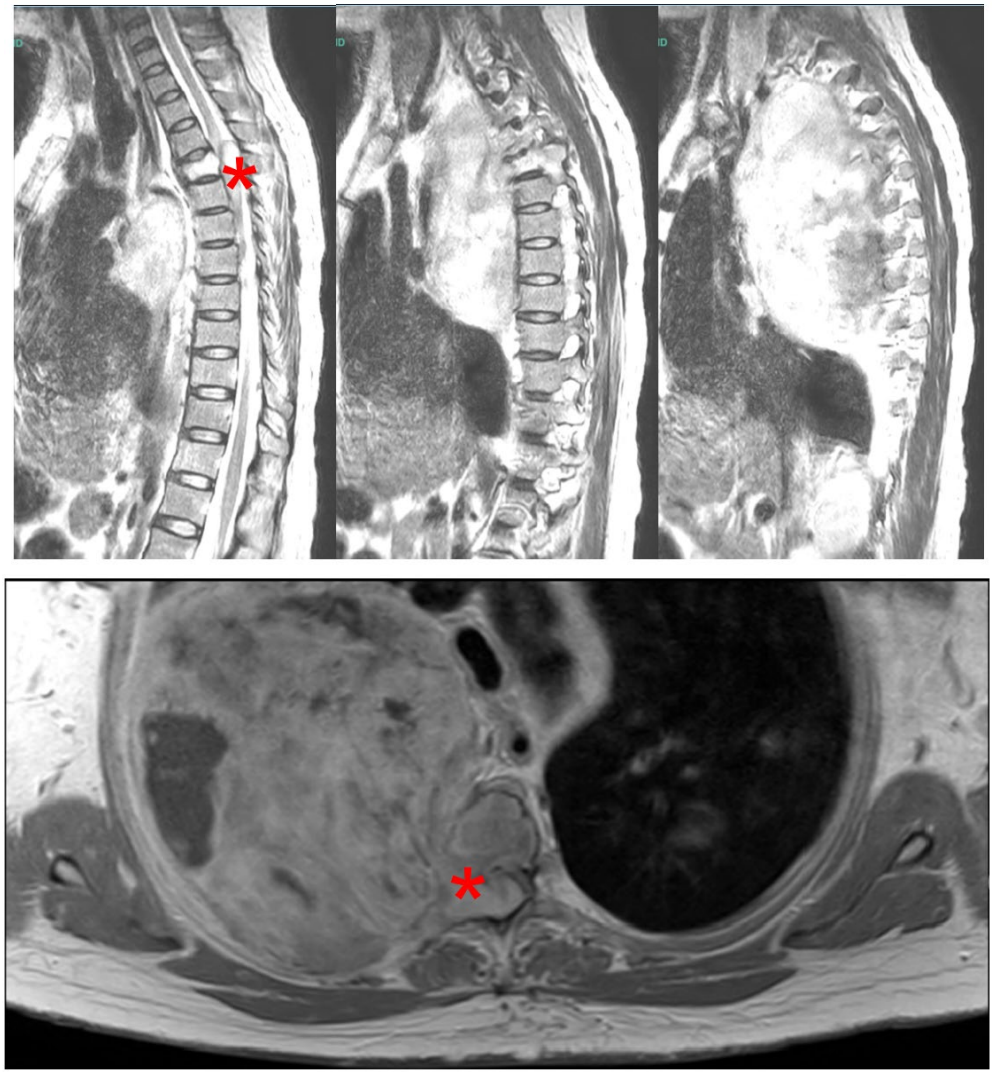

Figure 4. MRI with contrast sections showing a complex Neurofibroma with cystic component originated from intradural exiting through T3 - T4 foramina (asterisk) extending and obliterating the right posterior mediastinum compressing the right lung.

vasopressin) to ensure adequate blood pressure. She was managed as a case of Acute Respiratory Failure Type I and II from Hospital Acquired Pneumonia on top of Obstructive Pneumonia, Pulmonary Mass Right probably malignant, and was transferred to the Intensive Care Unit. Antibiotics were shifted to cefepime empirically. Subsequent imaging procedures suggested that the mass might indeed be a large neurofibroma arising from the thoracic peripheral spinal nerves going out all the way to the chest cavity.

Skin punch biopsy of nodules on her abdomen and forehead revealed a basketweave stratum corneum overlying an atrophic epidermis with basal layer hyperpigmentation; hyperproliferation of spindle cells with interspersed collagen bundles, mild interstitial and perivascular infiltrates composed of lymphocytes, histiocytes, and mast cells in the dermis. (*Figure 3*).

Ophthalmologic examination also revealed two Lisch nodules, approximately 1 mm in diameter, in the right iris.

An urgent thoracic Magnetic Resonance Imaging with A Thoracic Magnetic Resonance contrast imaging revealed a "large well-defined, lobulated, heterogeneous, intradural, extramedullary mass complex predominantly solid with cystic component seen at the level of the inferior endplate of T3 to mid of T5 vertebrae, causing a marked compression of the spinal cord at these levels with decrease in T2 signal noted. The solid component exhibits heterogeneous predominantly intermediate signal in T2, predominantly hyperintense in T2FS, hypointense in T1, with bright signals on post-gadolinium study. The cystic component exhibits T2/FS hyperintensity and T1 hypointensity with no enhancement on post contrast study. The mass

extended into the right posterior mediastinum through the right T3-T4 foramina with marked increase in size noted. It measured approximately 15.3 cm x 12.9 cm x 9.7 cm (CCWAP) seen from the level of the C6 vertebra superiorly and T9 inferiorly, causing an anterior and leftward deviation and compression of the trachea and right main bronchus, with no vascular or tracheal encasement and infiltration demonstrated.

Her ongoing infection, respiratory, and hemodynamic instability prevented her from undergoing Computed Tomography-guided biopsy of the pulmonary mass. Antibiotics were continued, and trial of weaning was started; however, she was unable to tolerate synchronized intermittent mandatory ventilation mode and then underwent conversion tracheostomy. Initial plans for a multidisciplinary team (MDT) meeting with Thoracic and Cardiovascular Surgery, Neurology, Neurosurgery, Orthopedics, and Interventional Radiology were made for possible surgical excision versus debulking of the mass.

To facilitate surgical planning, she underwent stereoscopic Computed Tomography of the whole spine was done which revealed a large 15.3 cm X 12.9 cm X 9.7 cm right posterior mediastinal mass, T3-T4 with ipsilateral neural foraminal and spinal canal infiltrations with T4 pathologic fracture. Secondary partial airway obstruction; minimal pleural effusion with passive lower lobe atelectasis, right; pneumonia with bronchiectatic changes, left. Acute long segment bland thrombus formation in the right internal jugular vein, jugular bulb, subclavian, axillary, and ovarian veins were noted. The findings of an extensive thrombus warranted anti-coagulation prior to surgery.

Two Multi-Disciplinary Team Meetings were conducted with a consensus for a 2-phase surgery with Phase 1 involves an initial resection and subsequent release of the Neurofibroma from its origin at T3 to T4 Vertebra by Neurosurgery through Right Hemilaminectomy of T3 - T4 via Lateral Extracavitary Approach with Costotransversectomy and Hemifacetectomy, and then stabilization of the spine by Orthopedics involving instrumentation with fixations of T1 - T3 and T5 - T6; Phase 2 involved resecting the mediastinal extension of the mass by Thoracic Surgery through Posterior Thoracotomy.

During the procedure and shortly after anesthetic induction, she was noted to have desaturations as low as 80% on FiO2 100% and hypotensive episodes. All services involved agreeing to defer the procedure. She was started on inotropic support with reversal of muscle relaxants.

A repeat MDT meeting was done once the patient was stabilized, with Anesthesiology revising their plans to perform bronchoscopy-guided single lung intubation prior to surgery. However, after months of hospital stay, the patient and her family came to believe that her was terminal then decided to refuse all possible surgical interventions and opted to go home against medical advice. The patient reportedly expired at her home 1 week after discharge.

Discussion

Neurofibromatosis Type I has an autosomal dominant pattern of inheritance with complete penetrance and variable expression. However, in 30-50% of cases, the condition arises from spontaneous mutation of the NF1 gene.[1] The incidence worldwide is 1 in 3000 live births, and is the most common among the neurofibromatoses.[2] Incidence in the Philippines is unfortunately not well documented, and the number of NF1 cases cannot truly be ascertained, though data from the Philippine General Hospital Department of Neurology reported 4 patients in 2022.[3]

Neurofibromatosis Type I is characterized by loss of function mutations of the NF1 gene, located on chromosome 17q11.2, which results in loss or reduced production of the protein product neurofibromin.[4] Neurofibromin, a guanosine triphosphate hydrolase activating protein (GTPase activating protein), regulates the activity of oncoprotein Ras by activating its intrinsic GTPase activity, thereby facilitating its inactivation via binding with guanosine diphosphate.[5] The dysfunction of neurofibromin, the Ras oncoprotein activates the mitogen-activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) pathways, allowing unrestricted cell proliferation[6].

The National Institutes of Health initially set a diagnostic criterion in 1987, which has helped identify patients with NF1 based primarily on clinical presentation. However, in 2021, a new international consensus was formed with a revised criteria for NF1 - "the diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 with two or more of the following are present: (1) Six or more cafe-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals, (2) Freckling in the axillary or inguinal region, (3) Two or more neurofibromas of any type *or* one plexiform neurofibroma, (4) Optic pathway glioma, (5) Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging, (6) A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone, (7) A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells". In addition, a child of a parent who meets the diagnostic criteria as specified above merits a diagnosis of NF1 if one or more of the criteria are present.[8]

The case presented met five of the diagnostic criteria. She only began experiencing symptoms at the age of 31 years, with rapid symptom progression in the next 3 years: evolving from bilateral lower extremity weakness to paralysis, loss of sensation, loss of bowel and bladder control, culminating with respiratory distress. Her intradural extramedullary mass extending into the

posterior mediastinum had already measured 15.3 cm x 12.9 cm x 9.7 cm. The same stereoscopic CT scan of the whole spine revealed an acute long segment bland thrombus formation in the right internal jugular vein, jugular bulb, subclavian, axillary, and ovarian veins.

In individuals presenting with signs and symptoms of NF1 in childhood, yearly surveillance visits are advised with comprehensive physical examination, ophthalmologic examination, and development of plexiform neurofibromas.[9] In adults, screening for malignant peripheral nerve sheath tumors (that arise from plexiform neurofibromas), breast cancer (with annual mammogram recommended starting 30 years of age), hypertension, and osteoporosis is done at yearly intervals; however, any new onset symptom should be investigated further.[10]

In neurofibromatosis type 1 (NF1), spinal tumors cause neurological symptoms in about 2% of patients. In a review of over 1400 patients with NF1, symptomatic spinal tumors are seen in only 22 or 1.6% of cases. There were 24 patients with symptoms such as sensory impairment or paralysis; 30 patients had no neurological deficits. Of the 24 symptomatic patients, 23 (96 %) had spinal tumors, while spinal tumors occurred in only 12 (40 %) of the 30 patients without neurological deficits.[11]

Dumbbell tumors are defined as those neurofibroma with significant intraspinal and paravertebral involvement. Most commonly present as intradural extramedullary neurofibromas, it can have different degrees of involvement of the spinal root, plexus, peripheral nerves, and end organs. They tend to occur most commonly at the cervical and thoracic levels; and less frequently lumbar level. Their sizes vary, but these lesions are generally larger in the lumbar spine. Clinical symptoms develop as a result of local compression of the ventral or motor nerve roots. Neurofibromas that extend outside of the spine would usually have larger extraspinal parts than the intraspinal portion and extend into the chest cavity causing compression and respiratory distress as seen in the case presented.[12] Extremely large tumors have lobular structures and may show cystic degeneration. The best imaging modality for evaluation of these lesions is through MR imaging where they appear in T1-weighted images obtained after administration of contrast medium as lesions with intense enhancement which may be uniform or heterogeneous, depending on the level of cystic changes; and are likewise usually hyperintense on T2-weighted images.[13,14]

Surgical approaches to spinal neurofibromas involving the thoracic spine must always be approached with great care. Although nerve roots can be sacrificed, surgical approaches to the upper and middle thoracic spine must avoid injury to the spinal cord and great vessels. Traditional approaches to the thoracic and lumbar spine result in long operative times and high morbidity for the patient.[15]

The surgical approach for treatment of a paraspinal neurofibroma depends on the location of the lesion and its relationship to the paraspinal anatomy. Indications for surgery include intractable pain and paresthesia, weakness, myelopathy, or spinal cord compromise. Patients with severe pain and paresthesia may benefit from resection and may experience significant improvement in symptoms. However, resections tend to result in a higher rate of permanent disability, and are less likely to improve given the expansive nature of the disease and the widespread involvement.[15]

Majority of the nerve fibers are entrapped by tumoral tissue in dumbbell neurofibroma cases as was the case in our patient as well. It is impossible to remove the tumor without sacrificing the nerve root and aggressive surgery may result in severe neurological deficits. Thus, partial resection should be preferred in dumbbell neurofibroma cases that cause compression of the spinal cord. The aim of partial resection is to relieve the symptoms, the extent of surgical treatment is based upon the clinical picture of the patient.[16]

Challenges encountered during the patient's surgery were the multiple complications attributed to the compression of vital structures by the mass. A consideration of Complete Spinal Cord Transection Syndrome from tumor compression was entertained when after the initial induction of anesthesia on one of the procedures, the patient manifested labile blood pressure despite low dose induction; with concurrent clinical picture of flaccid paralysis and loss of sensory modalities of bilateral lower extremities, absence of reflexes in the lower extremities, and loss of bladder and bowel tone. The apparent autonomic dysfunction created challenges on the options available for general anesthesia for the long and complicated surgery contemplated, and the option left was for regional anesthetic block which was challenging for the case.

During the first attempt at surgery, lateral positioning of the patient to ensure access caused respiratory distress, with desaturation attributed to the compression by the mass of the unaffected lung. This led to technical difficulties on the surgical approach and technique that was originally contemplated; an option to position the patient with the left lung up was planned but would make the surgery more complicated than it already was.

Extension of the mass into the mediastinal space also caused splaying at the level of the carina causing partial airway obstruction and made weaning from mechanical ventilatory support difficult. During the course of her admission, the patient persistently required pressure support on assisted ventilation. An extensive thrombus was seen in the Right Jugular, Subclavian, and Axillary veins requiring continuous anticoagulation before surgery to reduce the risk of embolization intra-operatively.

Taking into consideration all the technical difficulties and medical problems of the patient, discussions were made on the outcome expected, emphasizing the risks of the procedures involved, eventually with the patient and her family finally deciding not to go through with the procedures.

A similar case of a 34-year-old female was documented for a 7.4 cm × 6.3 cm × 6.1 cm extraspinal extension at the posterior thoracic cavity of a dumbbell neurofibroma originating from the upper thoracic level at T3 to T4. The patient only presented with progressive lower extremity weakness over the 3 months, then neurologic examination showed spastic paraparesis more pronounced distally, hypoesthesia below T3 dermatome, and hyperactive deep tendon reflexes. She underwent single stage posterior approach surgery, and recovered post-operatively with an uneventful course. The patient was able to walk without support and could perform routine activities after 2 months.[17] Extended literature search failed to show any thoracic neurofibroma larger than that of our patient's.

Expected outcome of treatment from complete excision of the intradural extramedullary neurofibroma varies depending on the size and location. These lesions are generally not excised unless they cause pain or neurologic symptoms, with the goal of treatment being symptom control.[18] Excision of a primary intradural extramedullary mass is associated with a 5 - year survival rate of greater than 65%.[19] However, tumor recurrence post-resection has been identified to occur more often in the setting of NF1, and has been identified as a risk factor for recurrence along with advancing age at diagnosis, subtotal resection, and malignant peripheral nerve sheath tumors.[20] Intradural extramedullary neurofibromas that have extraforaminal extension, as in this case, are associated with more complications often requiring spinal stabilization and sacrificing nerve roots and fibers, with permanent deficits.[21,22]

The prognosis for patients with dumbbell neurofibromas of the thoracic vertebrae, particularly those with neurological deficits, can vary based on the timeliness of diagnosis and surgical intervention. Neurological symptoms, such as motor weakness or sensory loss, may persist if there is prolonged spinal cord or nerve root compression before surgery. Early diagnosis and surgery are crucial in preventing permanent neurological damage. Studies suggest that although surgery can alleviate many symptoms, long-standing nerve compression may result in some permanent deficits. Since patients with NF1 have a higher chance of developing new neurofibromas, long-term follow-up is essential.[23]

A detailed examination of the patient's case allows us to pinpoint retrospectively where potentially life-saving interventions could have made significant difference in the outcome: early recognition of the patient's Neurofibromatosis Type I diagnosis could have already placed her on regular monitoring for potential complications of the disease and surgical resection before the development of neurologic symptoms could have improve the outcome with lesser technical and medical challenges precluding the surgery.

Conclusion

Patients with Neurofibromatosis Type I are able to live full lives with proper surveillance and immediate intervention on identified tumors when diagnosed early. Survival is generally 15 years less than the general population, with deaths commonly attributed to the development of massive tumors and malignancy in preexisting neurofibromas.[23]

The surgical treatment of neurofibromas involves their total removal. Since neurofibromas are commonly of root origin, this root must be found, dissected, or resected if necessary. The level of surgical intervention requires a multidisciplinary team, and should involve extensive neurophysiological testing to determine the degree of penetration and invasion of the spinal axis. The best results are obtained with patients showing minimal neurological deficits during the preoperative period.

This paper highlights the case of a 34-year old female who at birth already presented with the initial signs of NF1 who was however, seen by a multidisciplinary team only when the main neurofibroma has grown so large (the largest thoracic neurofibroma reported so far) and already compressed vital structures significantly, leading to challenges in the field of Internal Medicine, Pulmonology, Neurology, Neurosurgery, Thoracovascular Surgery, Vascular Anesthesia, and Orthopedic Surgery, leading to deferment of surgery and the eventual demise of the patient.

Conflict of Interest. The authors declare no conflict of interest.

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Ethical Statement. The patient and her family gave their informed consent for the documentation and publication of this study.

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