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Progressive Airway Obstruction due to Plexiform Neurofibromain 7 Years-Old Female

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Abstract: ***Background: Extention to larynx of Plexiformneurofibromasare extremely rare, approximately for only 0,03 to 0,1% of benign tumors of the larynx, it is one of neurofibroma type 1 (NF-1) variant.[1,6] Surgery is the only choice to achieve temporary tumor growth control and symptom progression. Patient with small plexiformneurofibroma eligible for complete resection of tumor. Case: 7 years old female presented with dyspnea. Physical examination showed a lot of subcutaneous neurofibroma. Endoscopy shown massive airway obstruction, that was narrowed by greater than 50% than decide emergency tracheostomy. Unfortunately, the patient getting worse because of progressive airway obstruction lower the site of tracheostomy and patient death because airway obstruction. Learning Points: Tumors location in head/neck/face cannot be completely removed, this tumor had been reported difficult to separate from normal tissue because they lack a well-defined capsule.Airway compression and spontaneous bleeding are direct lethal complication of plexiform neurofibroma.***

Keywords: neurofibroma, plexiform neurofibroma, airway obstruction

1. Introduction

Type 1 neurofibromatosis (NF 1) is a rare genetic diseasewith incidence of 1 in 4000 births. Neurofibromatosis has two distinct types which is neurofibromatosis type 1 and 2 respectively.[1] In type 1 neurofibromatosis,chromosomal defect occurred at the long chain of 17 chromosome, while in type 2 neurofibromatosis it is occurred at chromosome 22. These chromosomal defects put individuals at risk to developa variety of benign and malignant neoplasm.[2]

Plexiform neurofibroma is one distinct variant of type 1 neurofibromatosis, more than 50% clinically occurred in the region of the head, neck, face and larynx.[1,2] Plexiform neurofibromas has tendency to be locally invasive which triggered cosmetic deformities as well as functional deficits. Type 1 neurofibromatosis are peripheral nerve sheath tumor which contains elements of peripheral nerve.It is characterized by accumulation of endoneurial matrix along with separation of nerve fascicles and proliferation of Schwann cells. Macroscopically the tumors are diffusely infiltrative, also known as “bag of worms” morphology. Plexiform neurofibromas may transform to malignant neoplasm with rate of 4% to 5%.[3]

Usually, plexiform neurofibroma will be managed surgically. Plexiform neurofibroma are not radiosensitive and only yield limited benefit from chemotherapy. Greatest risk of recurrence is found for lesions involving the region of the head and neck also in pediatric population younger than 10 years old.[4]Controversies persist regarding the topic of surgical indications and timingof the head and neck plexiform neurofibroma. Most otolaryngooncologist will be reluctant to undertake resection, given the high rate of local recurrence and the potential for postoperative cosmetic as well as risk of functional morbidity.[5] In practice, the tumor will be managed conservatively, unless the tumor is easily resectable, without risk of resultant neurological dysfunction. Serial imaging studies is needed to determine impending risk of airway obstruction or other issues related to critical neck structures.[6] The aim of this report to describe a rare case of plexiform neurofibroma on neck and already done tracheostomy but the airway obstruction still happened progressively.

2. Case Report

We reported a case of massive neck plexiform neurofibroma with intralaryngeal extension in a 7-year-old girl with neurofibromatosis type 1. The disease started when she 3 years old with the appearance of multiple hyperpigmented skin macules. At the age of 4 a lot of cutaneous tumor appeared and started to increase in size all over the body surface especially on right neck. The growth of the fibroma on her neck continue until half of her chest. There aren’t any complaints until she 7 years old, when she came to hospital for the first time because she experiencesdyspnea, the parent said that her children usually difficult to sleep because hard to breathe, she also experiences throat discomfort on swallowing with no change voice, hemoptysis, pain cough or snoring. At first, she treated as pneumonia but the symptom seems not resolved perfectly. Her father suffered this condition too but there aren’t significant symptomatic neurofibroma on him.

On physical examination showed a moderately built and nourished child with steady gait and satisfactory vital sign. There were no sign icterus, clubbing or anemia. No neurologic or ophthalmologic symptoms were evident. There is a lot of soft cutaneous neurofibromas, hyperpigmented skin almost half of her body (>6 patches). Soft cutaneous neurofibromas ranging from a few millimeters to several centimeters in diameter, some of them pedunculated, multiple café-au-lait spot with diameter 1,5 cm. The mucous membranes were not affected. No axillaryor inguinal freckling, superficial neurofibroma or Lisch nodules were evident, as might be expected in NF1. Audiological evaluation was normal for both ears. She had a history of intermittent stridor, which was managed supportively.

Neck examination revealed large, diffuse and soft swelling in the right neckwith ill-defined edges with no redness, hotness, tenderness, superficial vessel, pigmentation or ulceration. There were no palpable cervical lymph nodes. There is stridor on expiration.

Opthalmological status with Linch's nodules on the iris of both eyes were without clinical visual involvement. The standard laboratory test values were in the normal range. Neurologist did not detect alteration in the central and peripheral nervous system. According to the otologist the acoustic nerve has not been damaged.

The dermis layer contains an unlimited tumor mass, consisting of loosely-proliferated cellular cells, between connective tissue and skin adnexa. The cells with morphologic boundaries between cells are unclear, the core is oval to spindle, wavy, fine chromatin, regular core membrane.

Imaging revealed bone deformityand massive cervical spine plexiform neurofibroma that caused external compression of thehypopharynx, visualized by endoscopy. She required urgent placement of a tracheostomy tube at the time of diagnosis because her airway was narrowed by greater than 50% of the subglottic space. No extirpative surgery was undertaken owing to concern over the potentially large operative morbidity. She also already done echocardiography procedure, then the result shown mild cardiomyopathy and she got anti failure consist of furosemide, spironolactone and digoxin and done serial echocardiography evaluation. From that serial evaluation the echocardiography shown better.

Diagnosis of neurofibromatosis type 1 was made according to the presence of four of the seven diagnostic criteria of the National Institute of Health Consensus Development Conference as follow five or more café-au-lait spot larger than 5 mm in diameter in prepubertal patients, two or more neurofibromas of any type or one plexiform neurofibroma, axillary or inguinal freckling and two or more Linch's nodules.

Patient already admitted in Hospital for several days than she felt difficulty in breathing more prominent, from endoscopy shown airway obstruction, there were extra thoracic and intrathoracic trachea was narrowed from 2,5 cm below the larynx to the carina with luminal narrowing from both lateral aspects so on that time decide emergency tracheostomy had to be performed. After getting a precise idea about the extent of the lesion and histopatological diagnosis, second surgery still on doubt. Biopsy samples were taken and no malignant cells were found. Location and tumors extensionwere high risk for operation, after tracheostomy patient was observed in intensive ward, but dyspnea wasn't getting better. Patient getting worse although already done tracheostomy, there was progressive airway obstruction lower the site of tracheostomy. Resuscitation already done but the patient didn't get better and there after the patient death because of airway obstruction.

3. Discussion

Neurofibromatosis is an entity that have been observed for a long time, firstly described by Robert William Smith in 1849. The most prominent classicalcase description is made by German pathologist, dr. Frederich Daniel von Recklinghausen. He accurately described the diverse clinical finding as a single entity known to be NF in year of 1882.Since then, the condition is referred as von Recklinghausen's disease.[1]

Until now, there is no single accepted classification for neurofibromatosis. Most commonly, there are four forms of neurofibromatosis including the Von Recklinghausen's neurofibromatosis (NF 1), bilateral acoustic neurofibromatosis (NF 2), segmental neurofibromatosis and cutaneous form of neurofibromatosis.[2] Neurofibromatosis consists of at two separate genetic disorders, characterized by the tumor formation surrounding nerves cells and many other histopathological features. Recently, six additional types have been proposed.[1,3]

NF-1is an autosomal-dominant disorder with prevalence approximately of 1 in 3000 to 1 in 5000 births.NF-1 is known as one of the most common autosomal-dominant entity. Due to its high mutational rate, the penetrance of NF-1 gene with a clinical presentation of the disorderis nearly 100%, and more than 50% of newly diagnosed cases may resembles new mutations.[1,3]It is proved that the gene is located to the proximal long arm of chromosome number 17. Clinically, there are 4 different type of NF-1, including discrete cutaneous neurofibromas of the dermis or epidermis, subcutaneous neurofibromas, deep nodular neurofibromas, and diffuse plexiform neurofibromas.[3] Plexiform neurofibroma characterized by spread of tumor cells along multiple nerve fascicles, resulting a diffuse mass of thickened nerve fibers and surrounded by proteinaceous matrix. Clinically, plexiform neurofibroma can be located superficially or deeply seated, or in some cases, a combination of the two locations.[2]

NF-1is clinically characterized by multiple café-au-lait spots, accompanied by the occurrence of neurofibromas along the peripheral nerves. Cutaneous neurofibromas often seen as soft, flesh to lilac-pink-colouredtumours, or in the form of sessile or dome-shape, also pedunculated form, and most frequently encountered on the trunk and limbs. Other significant hallmarks include Linch's nodules (melanocytic pigmented iris hamartomas) or oral lesions. Several possible complicationsof NF-1 in pediatric population include therisk of optic glioma, hormonal/endocrine disturbance or lower urinary tract involvement of the disease. Learning disabilities were also found in several cases.[3]

Plexiform neurofibromas has no ability to metastasize and usually locally invasive thatmanifested on the skin or peripheral nerves.[4]It is also having capability to grow invasively including the extension into intralaryngeal space. Laryngeal involvement of neurofibromas are extremely rare, approximately accounts of 0,03 to 0,1% of benign laryngeal neoplasm. Histopathologically, several subtypes of neurofibromas exist, includes cutaneous, subcutaneous, nodular, and diffuse plexiform variants.[5]In the other hand,

case of confirmed endolaryngealneurofibroma have been reported in the English literature dated 1950 (Hollinger). Most of the endolaryngealneurofibromacases have been reported occurred in the pediatric population and in associated to NF-1.[3,4] Our case showed characteristic of plexiform type with involvement of deep neck spaces and intralaryngeal extension.

Until recently, neurofibromas have been reported to be surgically difficult to managed, due to lack a well-defined capsule and are usually made up of a mesh of interwoven spindle cells, axons, enmixed with collagen fibers. Extensive tumors growth may be associated with significant bleeding in several cases. Laryngeal neurofibroma proposed to be arises from the superior laryngeal branch of the glossopharyngeal nerve.In our case, the plexiform neurofibroma was relatively massive, with extension to the lower neck, and its surgical resection was complicated to be performed.[5-7]

In type 1 neurofibromatosis there are some defect in the long chain of chromosome 17, and in type 2 neurofibromatosis, the defects are located in chromosome 22. The NF-1 gene was historically cloned on chromosome 17q11. The gene product known as neurofibromin, is ubiquitously expressed at high levels in the nervous system and it is having a property of tumor suppressor genes. Loss of neurofibromin through mutation, leads to an increased risk of developing benign and malignant neoplasms in vulnerable individuals.[2,3]

According to The National Institute of Health (1987), NF-1 is diagnosed clinically based on its clinical manifestation. There should be 2 or more signs and symptoms from 7 criteria: 6 or more *café au lait*macules (>0,5 cm n children or > 1,5 cm in adult), 2 or more cutaneous/ subcutaneous neurofibromas or one plexiformneurofibroma, axillary or groin freckling, optic pathway glioma, 2 or more Linch nodules (on slit lamp examination), bony dysplasia (sphenoid wing dysplasia, bowing of long bone ±pseudoarthrosis), and first degree relative with NF.[1]Genetic testing (gene mutation analysis) is not routinely recommended and expert consultation is advised. Biopsy of asymptomatic individual with cutaneous lesion should not be undertaken for diagnostic purposes for case with clearcut NF-11.[1,2]

Clinical manifestation of plexiform neurofibroma is depends to tumor size and location. The lesion potentially compresses vital organs and may result in severe morbidity or mortality. Surgical interventions were required in many cases and resulted in added morbidity in some cases.[7,8]Khosrotehrani et al showed that high risk for mortality of NF 1 case is related to absence of cutaneous neurofibromas and facial asymmetry.[8] Tumor progression is a significant problem to be addressed, especially for pediatric plexiform neurofibroma case, younger age, or pediatric case with head/neck/face tumors and the on that cannot be completely surgically removed.[9,10] NF-1 clinical manifestation often affects on the day-to-day functioning of thepatientssignificantly, both from individual perspective as well as parental aspects.[11]

Mortality is associatedindependently with the presence of subcutaneous neurofibromas (OR 10,8; 95% CI 2,1-56,7; p<0,001), the absence of cutaneous neurofibromas (OR 5,3; 95% CI 1,2 – 25; p=0,03) and facial asymmetry (OR, 11,4; 95% CI 2,6-50,2; P<0,01). Prevalence of clinical manifestations of NF-1 is influenced by patient's age (number of cutaneous neurofibromas increased with age, number of café au lait spot decreases). It is believed that sub-cutaneous neurofibroma form arise along the peripheral nerves beneath the skin which has characteristic of firm to palpation. Clinically the lesion can be found as beadlike nodules along the length of nerve. Tumor arise from spinal nerve root may grow through the neural foramen, forming a dumb-bell shape that leads to nerve root or spinal cord compression. Presence of subcutaneous neurofibroma can be associated with the co-presence of profundal nodular neurofibromas that if occurred adjacent to vital organs,maytriggeredmechanical obstruction or compression. As stated before, facial asymmetry is one of mortality risk factor. It is related tothe cranial and facial bony dysplasia in sphenoid bone. It is also associated with intracranial tumors which may cause substantial morbidities and mortality.[7] Until now, risk factors that shapedits phenotype are unable to be identified. Phenotypic similarities observed in families with NF-1 are consistent with the hypothesis that modifying genes influence the NF-1 phenotype.[9]Neurofibromin may interacts with other proteinsincluding tubulin, kinase, and Ras. Functional variants of these proteins might also influence the NF-1 phenotype.

Surgical intervention is the only modality that has been shown to achieve temporary tumor growth control with significant symptom progression. Complete resection is only possible in small plexiform neurofibroma lesion.[6]

Tumor progression should be considered seriously in pediatric population, the lack of well-defined capsule and internal property composed of interwoven spindle cells, axons, and collagen fibers make it more difficult to be completely removed and thus warrant more aggressive progression, and may associated with massive internal bleeding.[5]Patient's age, lesion location, extent of surgical resection are statistically significant predictors of tumor recurrence. Patient under 10 years-old had a higher incidence of tumor progression after first surgical procedure, while children with older age was associated with longer interval to progression. Lesion's location is also an important prognostic factor. Tumors located in the head, neck, and facialarea has a high likelihood for progression, and tumors located in the extremities were significantly less likely to progress, while the one that located on the trunk were intermediate risk.Extent of surgical resection was also of prognostic significance.Greater extent of surgical resection found to have lower risk of progression and longer interval to tumor progression.[10]

Mortality rate in pediatric patients with NF-1 with plexiform neurofibroma is higher compared to patients without known/asymptomatic plexiform neurofibroma. Airway compression and spontaneous internal bleeding two of the most lethal complication. Surgical interventions which were often clinically required, may often resulted in added morbidity to the patients. Due to the potential for lethal complications, these findings suggest the need for effective

medical management for plexiform neurofibroma. Patient with plexiform neurofibroma have a higher risk for developing additional NF-1 associated tumors, and careful clinical monitoring is warranted.[6]

4. Summary

Our caserevealed a plexiform type neurofibroma involving the deep neck spaces with intralaryngeal extension**.** The patient was referred to our hospital with chief complaint dyspnea.On physical examination showed a lot of soft subcutaneous neurofibromas, hyperpigmented skin almost half of her body (>6 patches). Soft subcutaneous neurofibromas ranging from a few millimeters to several centimeters in diameter, some of them pedunculated, multiple café-au-lait spot with diameter 1,5 cm, there is facial asymmetry, superficial neurofibroma or Lisch nodules were evident, as might be expected in NF-1 that the histological result confirmed the diagnosis of neurofibromatosis. During hospitalization she experienced progressive airway obstruction. She already done tracheostomy but the condition didn't get better. Patient finally deceaseddue to lethal-progressive airway obstruction.

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