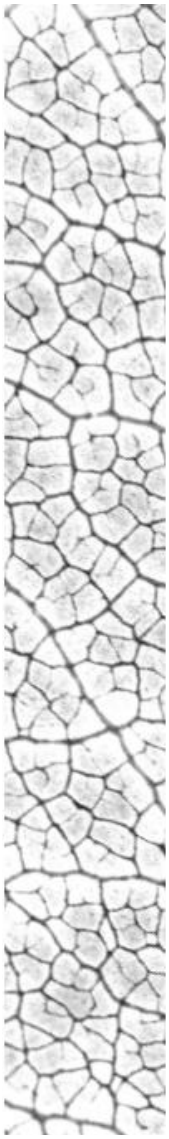

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Rare case report: Female patients of mediastinal neurofibroma without von Recklinghausen's disease

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Abstract

Background: The cases of mediastinal neurofibroma tumors without von Recklinghausen's disease are very rare. Clinical manifestations of tightness that do not get better with prolonged treatment using bronchodilators and steroids. After further examination and patient's history, a diagnosis of mediastinal mass can be established, that suppress the respiratory tract. **Purpose**: aim to know female patients of mediastinal neurofibroma without von recklinghausen's disease. **Method:** Old adult patients who experience mediastinal neurofibroma tumors with symptoms of shortness of breathing that are increasingly aggravated especially when cold and fatigue. Symptoms are related to compression or invasion directly to structures around the mediastinum or associated with paraneoplastic syndrome. Asymptomatic patients are usually associated with benign tumors and vice versa patients with symptomatic usually associated with malignancy. **Result**: The development of a malignant tumor occurs in 10% of cases of neurofibroma especially in patients with neurofibromatosis (von Recklinghausen's disease). The duration of ongoing disease coupled with complication from other diseases makes different alternatives the best indication. **Conclusion**: This tumor had reached the stage of surgical therapy to achieve safe and completed tumor excision. This therapy was carried out as an optimal effort to obtain a better prognosis for the patient's disease

Keywords: Mediastinum Neurofibroma tumors, severe tightness, surgical therapy

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INTRODUCTION

The prevalence of mediastinal neurogenic tumors is about 20-30% of all mediastinal tumors. Benign tumors are classified into two, namely schwannoma and neurofibroma (John, Larry, 2008). Schwannoma is the most common type of tumor (57.5%) and neurofibroma is a very rare case (18.9%). These two tumors usually develop in the posterior mediastinum (96.7%), and originate from intercostal, sympathetic or sometimes nerve vagus (Saito, et al. 2004). Almost all of these tumors are benign (70-80%), asymptomatic (40%), and found incidentally when checking routine x-rays (Rahman, et al. 2005).

The symptoms are usually related to compression or invasion directly to structures around the mediastinum or associated with paraneoplastic syndrome. Symptoms can include chest pain, coughing, tightness or neurological disorders. Asymptomatic patients are usually associated with benign tumors and vice versa patients with symptomatic usually associated malignancy (Divisi, et al. 1998). Chest CT scan is considered the main diagnostic modality in patients with posterior mediastinal tumors. however magnetic resonance imaging (MRI) can be best if there is an extension to the intraspinal area (Landwehr, Schulte, & Lackner, 1999).

The progression of a malignant tumor occurs in 10% of cases of neurofibroma especially in patients with neurofibromatosis (von Recklinghausen's disease) (Gawlewicz-Mroczka, Mastalerz, & Niżankowska-Mogilnicka, 2009). So surgical therapy is indicated in the majority of patients because of their ability to excise completely. If it can be perfectly excised, the patient will have a good prognosis (Duwe, Sterman, & Musani, 2005). We will report the case of a woman with a mediastinal neurofibroma tumor without von Recklinghausen's disease with clinical manifestations of tightness that did not get better even with prolonged treatment using bronchodilators and steroids. After further examination and history, a mass in mediastinal can be established, that suppress the respiratory tract.

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Table 1. Completed Blood Laboratory Results of Pre Surgery

WBC	16,900	**Natrium**	142	**pH**	7.46
Granulosit	86.1 %	**Kalium**	2.7	**pCO2**	34.8
Hb	12.0	**Klorida**	99	**pO2**	167.4
PLT	228,000	**CRP**	12.72	**HCO3**	25
BUN	18.54	**PPT**	21.5	**BE**	0.9
SK	0.65	**Control PPT**	26.5	**SO2**	99.6 %
Albumin	3.9	**APTT**	9		
GDA	635	**Control APTT**	11.2		
SGOT	18				
SGPT	26				

Table 2. Completed Blood Laboratory Results of Post-Surgery

WBC	8,780	**GDP**	187
Granulosit	58.9%	**SGOT**	24
Hb	10.6	**SGPT**	26
Plt	161,100	**Na**	136
BUN	4	**K**	3.4
SK	0.6	**Cl**	104
Albumin	3.4		

RESULT

Case Report

A woman named Mrs. D, 59 years old, a Javanese, Muslim, works as a housewife, having her address at Pandu Gresik. The patient was referred to Dr. Soetomo Hospital on August 4, 2014 with the main complaint of shortness of breathing since 2 weeks before being hospitalized and burdensome since 1 week before being hospitalized. Shortness of breathing appeared especially when cold and tired. Coughing for 2 weeks before being hospitalized with white phlegm and difficulty to be coughed up. It was obtained of chest pain complaints on the right. Subfebris fever was felt by patient since 1 week before being hospitalized. Patients complained of decreased appetite 1 week before being hospitalized. Complaints of weight loss, night sweats were denied by the patient. In the past 4 weeks, complaints of coughing, shortness of breathing, wheezing were almost experienced daily by the patients. And complaints of often awake in the night 3-4x / week and limited activity due to chest tightness.

Previously, patient was hospitalized in Gresik Hospital in 2011 due to shortness of breathing and diagnosis of tumors, then was referred to Dr. Soetomo Hospital for surgery but the patient refused. Patient was hospitalized at the Surabaya private hospital for 3 days and was referred to Dr. Soetomo Hospital due to increasingly shortness of breathing. Patient had suffered from asthma since she was young and used the salbutamol drug if asthma relapsed. She only went to the doctor if asthma was felt to have no improvement with the medication she consumed. The patient had suffered of Diabetes Mellitus since 7 months ago but did not routinely control the doctor. The patient also suffered from hypertension since 1 year ago and was not routinely in control. History of anti hypertention drug use was denied.

Physical Examination

The results of physical examination, the blood pressure was 150/90 mmHg, pulse was 120x / minute, breath frequency was 30x / minute, and axillary temperature was 37 ° C. The patient came in good general condition; consciousness was compos mentis. On head and neck examination, dyspnea was found, there was no anemia, jaundice or cyanosis. There were no abnormalities of eye, head, increased jugular veins or enlarged lymph nodes.

In the thoracic region, from the inspection there was a symmetrical chest shape, symmetrical chest movement, and no collateral veins appear. In palpation, fremitus is symmetrical. On percussion sonor was obtained in both hemitoraxes. On auscultation, vesicular breath in the right and left hemithorax was obtained, and rhonchi and wheezing were obtained in the right and left hemithorax. On a heart examination, single heart sounds (S1 and S2) examination,there was no heart noise or gallop rhythm.

On examination of the abdomen, liver and spleen were not palpable. There was no intra-abdominal mass and tenderness, and bowel sounds was in normal limits. The limb examination was warm, dry, red and there was no edema or other skin abnormalities. There was no enlarged lymph nodes in the armpit or thigh fold.

Laboratory Examination

See **Tables 1**-**3**.

Table 3. CT Scan and Radiography Results

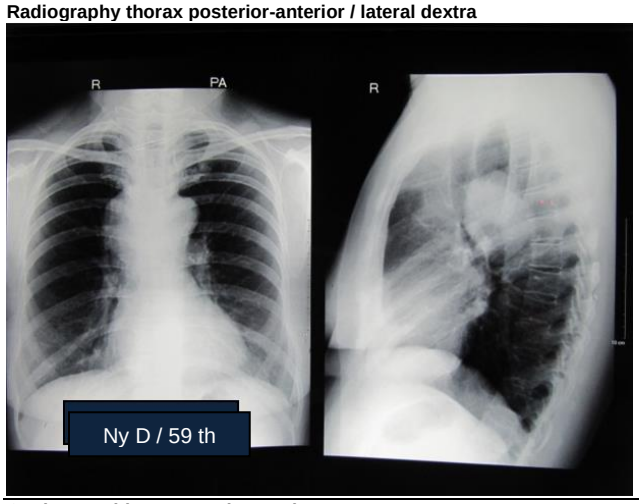
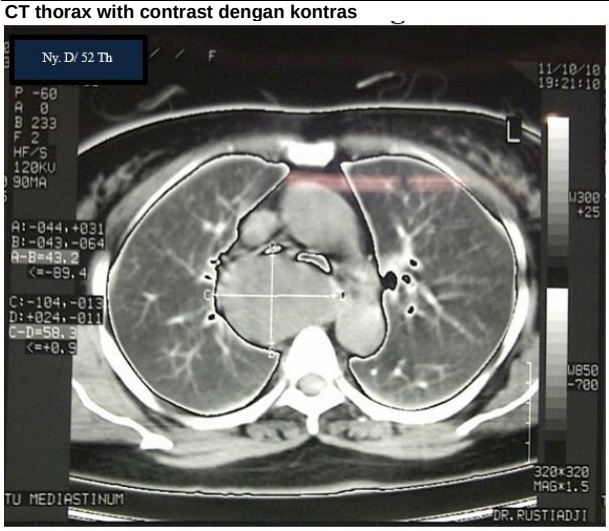
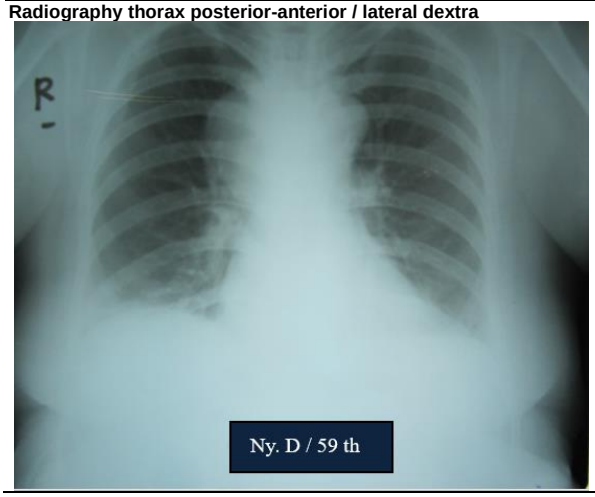
Laboratory results	Date of examination	Conclusion
Radiography thorax posterior-anterior / lateral dextra 	January10, 2011	Suspected a tumor in right mediastinum posteromedial
CT thorax with contrast dengan kontras 	October 12, 2011	The benign mediastinal tumor seems to be a neurinoma
Radiography thorax posterior-anterior / lateral dextra 	August 3, 2014	The image of mass in mediastinum medius to posterior

Table 3 (continued). CT Scan and Radiography Results

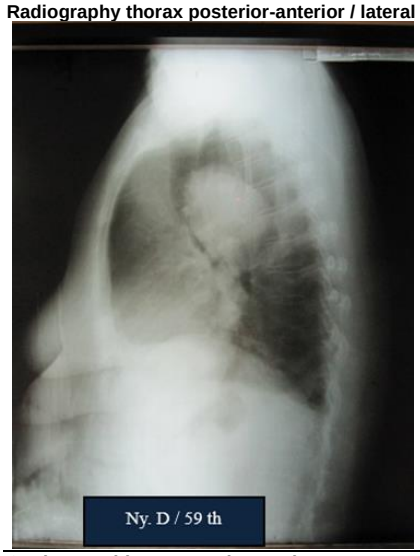
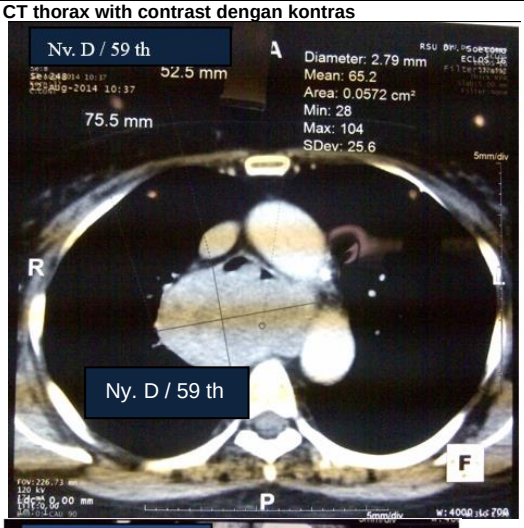
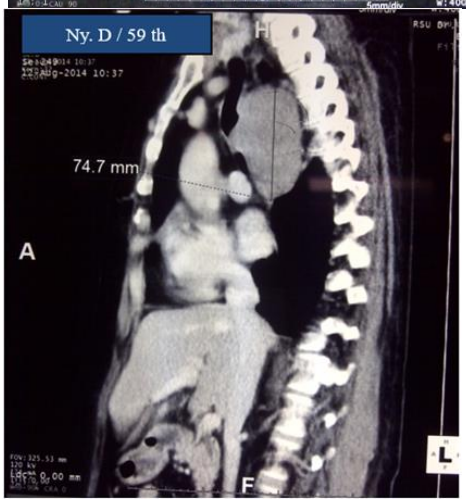
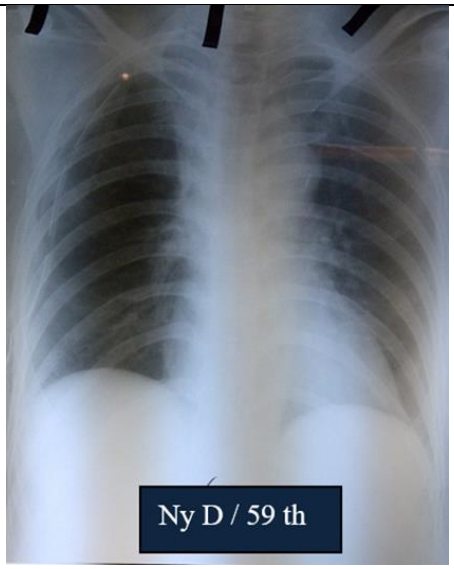
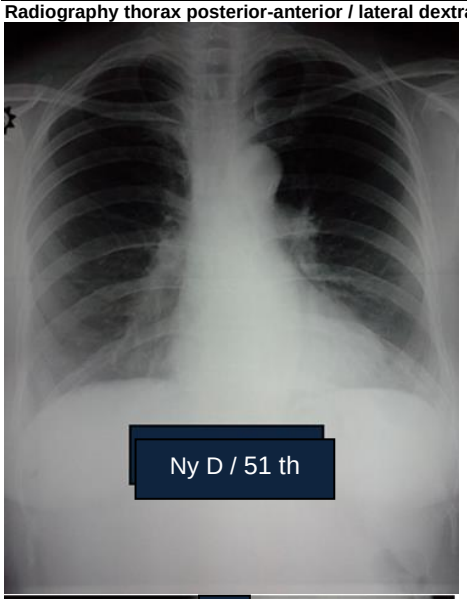
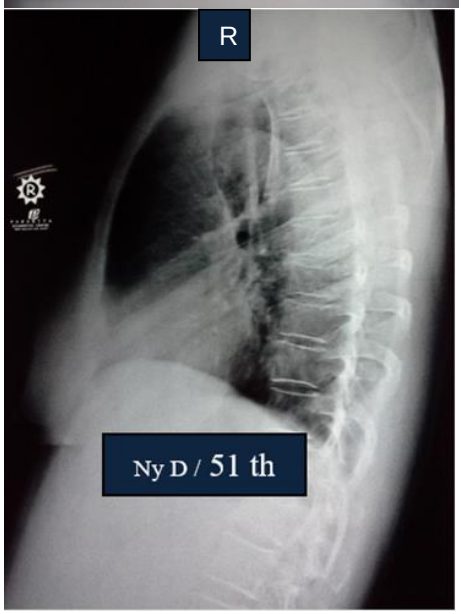
Laboratory results	Date of examination	Conclusion
Radiography thorax posterior-anterior / lateral dextra 	August 3, 2014	The image of mass in mediastinum medius to posterior
CT thorax with contrast dengan kontras  	August 12, 2014	A suspected mass in mediastinal of the right side of aortosclerosis

Table 3 (continued). CT Scan and Radiography Results

Laboratory results	Date of examination	Conclusion
Radiography thorax post surgery 	August 25, 2014	Mediastinum , operative : Neurofibroma
Radiography thorax posterior-anterior / lateral dextra ; post-surgery  	September 22, 2014	There is no abnormality

The case post-surgery

Patients complained a pain and feeling a heat in the area around the operating wound and tube insertion. Patients in full awareness with GCS 4-5-6 but general condition was weak. The results of blood pressure were 130/60 mmhg, pulse was 100x minutes, respiratory rate was 24x / minute and axillary temperature was 38 degrees Celsius. Normal bowel noise was heard.

The patient's breathing ability is supported by a 3 liter nasal O2 injection. The treatment therapy obtained by the patients was phosphomycin 2 x 2 gram iv, injection novorapid 3x16U sc ac, levemir 0-0-16U sc, ketorolac drip 2 x 1 ampoule amlodipine 5 mg - 0 - 0, codeine 3x10 mg po, chest tube + WSD - 20mmH2O, chest physiotherapy, B1 diet 2100 kcal.

DISCUSSION

Neurogenic tumor is the most common cause of posterior mediastinal mass and very rare. There is around 20% - 30% of all types of mediastinal tumors where almost this type is benign (70-80%) (Ribet, & Cardot, 1994). Schwannoma and neurofibroma originate from peripheral nerves. Schwannoma is the most common type of tumor (57.5%) and neurofibroma is a very rare case (18.9%) and often associated with von Recklinghausen disease (neurofibromatosis type 1). Multiple neurogenic tumors are usually synonymous with neurofibromatosis type 1 (Gawlewicz-Mroczka, Mastalerz, & Niżankowska-Mogilnicka, 2009). Schwannoma and neurofibroma are benign, grow slowly and often arise from the spinal nerve roots, but sometimes involve the thoracic nerve. 10% of neurofibroma in patients with von Recklinghausen's disease becomes malignant (Brzeziński, & Kozak, 2015) If it occurs at a young age it will increase the risk of becoming malignant (Strollo, Rosado-de-Christenson, & Jett, 1997). In this case the patient was at 59 years of age.

Neurofibromatosis type 1 (NF1) or it usually name as Von Recklinghausen is an autosomal dominant disease which genetically inherited by NF1 gene mutation (Koichiro et al., 2012) Based on NF1 NIH Consessus Conference Criteria 2007, NF1 diagnosed if there's two or more criteria (Gawlewicz-Mroczka, Mastalerz, & Niżankowska-Mogilnicka, 2009). There are no criteria entered for this patient.

Almost half of mediastinal tumor cases do not cause symptoms, including neurofibromas and if they appear they are usually non-specific (John, Larry, 2008). If symptoms appear they are usually malignant cases (Gawlewicz-Mroczka, Mastalerz, & Niżankowska-Mogilnicka, 2009). Based on the location of the mass, the patient may feel symptoms related to irritation and / or deficits related to compression or infiltration of the brachial plexus and cervical ganglion namely in the form of cough and chest pain (Shakoory et al., 2004). Chest pain, dysphagia and tightness can be caused by local tumor secondary symptoms which are from tumor invasion, so that the size of the tumor has caused anatomical distortion of the mediastinum. Systemic symptoms such as heat and weight loss are usually associated with hormones, cytokines and antibodies secreted by the tumor (Gawlewicz-Mroczka, Mastalerz, & Niżankowska-Mogilnicka, 2009).

In this patient, shortness of breathing symptoms have been obtained since 2 weeks before being hospitalized and burdensome since 1 week before being hospitalized. Shortness of breath appears especially when cold and tired. Coughing for 2 weeks before being hospitalized with white phlegm and difficulty to be coughed up. In the past 4 weeks, complaints of coughing, shortness of breath, wheezing are almost daily. And complaints often awaken in the night 3-4x / week and limited activity due to tightness. Obtained chest pain complaints on the right. Patient had a history of asthma with trigger factors, especially cold and tired. The excess number of mast cells will worsen and become a source of mast cells in neurofibroma. Asthma is characterized by exfoliating epithelial skin, activation of mast cells, influx eosinophils and the entry of inflammatory cells, and airway obstruction. Mast cells play an important role in the pathogenesis of asthma and inflammation. Mast cells are very potent and have many granules that will respond when stimulated with antigens.

One important aspect of the biological properties of mast cells is their ability to initiate and regulate an effective immune response by regulating eosinophil activation and recruitment. Mast cells also release a number of cytokines, for example, IL-3, IL-5, and GM-CSF, which will improve eosinophil survival and function. Eosinophils themselves are important in a number of allergic diseases, including asthma and parasitic invasion. Eosinophils can release many cytokines and chemokines that worsen the immune response (Sakai, et al. 1992). Neurofibromas consist of many types of cells including schwann cells, mast cells, fibroblasts, endothelial cells, and perineural cells. Under normal circumstances, mast cells come from progenitors in the bone marrow, then circulate in peripheral blood and then migrate to peripheral tissues (eg the lungs, digestive tract or skin) where they grow either into mucosal mast cells or mast cells connective tissue. Wei-Chun et al. has shown evidence that the chemokine CCR3 receptor and CCL7 ligand play an important role in the migration of mast cells to neurofibromas, and will even be able to maintain mast cell survival (Tai, et al. 2010). On the other hand the CCR3 also has a role in moving mast cells in the pathophysiology of asthma. Das et al. also has shown that small antagonistic molecules against CCR3 which can selectively inhibit the entry of eosinophils into the lungs and inhibit inflammation with allergies (Das, et al. 2006).

Asthma has a potential risk for the progression of proinflammatory conditions, one of which is Type 2 Diabetes Mellitus. The most probable mechanism regarding the relationship between asthma and Type 2 Diabetes Mellitus is genetic pleiotropy (one gene defect that gives rise to several disease phenotypes), pulmonary inflammatory cytokines, and their effects on insulin sensitivity, direct effects of hypoxia on glucose metabolism (Mueller, et al. 2013). Asthma is associated with increased nuclear factor interleukin-6 (IL6), tumor necrosis factor-α (TNFα), and molecular adhesion that will activate nuclear factor-κB. The level of inflammatory cytokines in this circulation is closely related to the risk of Type 2 Diabetes Mellitus (Liu, et al. 2007). Hypoxia and intermittent hypoxia hypoxia are also common in obese asthma. This situation will worsen glucose metabolism related or not related to insulin mediation. Some disorders of glucose metabolism can mediate the expression of proinflammatory cytokines or the formation of reactive oxygen species (ROS) which can suppress insulin secretion and worsen insulin sensitivity. (Bloch-Damti, & Bashan, 2005). In contrast, Type 2 Diabetes Mellitus patients will experience 3–10% reduction in pulmonary function (FVC and FEV1) compared with no Diabetes Mellitus, regardless do you have obesity and / or smokers. Poor and prolonged sugar control in Diabetes Mellitus disease will also worsen pulmonary function (Fernandez, & García, 2013). So it is likely that these patients have suffered from asthma for a long time which is exacerbated by mechanical pressure and active mast cells by neurofibroma which will eventually trigger the onset of Type 2 Diabetes Mellitus.

Besides that, after this patient experiences Type 2 Diabetes Mellitus, the use of synthetic corticosteroids for the treatment of asthma will have the same effect as endogenous steroids, which in addition to the activation process of anti-inflammatory proteins also modulates carbohydrate metabolism through its influence on beta cell function and induces insulin resistance in insulin receptors in the liver, muscles and fat tissue causing hyperglycemia. And in the end it will aggravate the Diabetes Mellitus. So that in patients with Type 2 Diabetes Mellitus with insulin therapy who get additional corticosteroid therapy synthetic it is recommended to increase the dose of insulin rapid acting at lunch and dinner and transfer of administration of basal insulin to the morning with an increase in doses of 2-4 units every 24-48 hours according to monitoring desired blood sugar level (Faul, et al. 2009. Varma, et al. 1992).

Radiologically neurofibroma is very similar to the imaging of adenocarcinoma, so that some clinicians perform repeated bronchoscopy with 'brush' and transbronchial biopsy with negative pathological results for tumor cells. Sometimes even with the help of CT guiding, the diagnosis does not lead to neurofibroma (Gawlewicz-Mroczka, Mastalerz, & Niżankowska-Mogilnicka, 2009). In general, chest radiographs will show a round, well-defined mass. If it is close to the bone, it can cause erosion and deformity in the ribs. Calcification is very rare in chest radiographs. On regular CT scans, punctate calcification diets other than features of hypocellularity, cystic changes, bleeding, or the presence of lipids in the myelin (Uchida, et al. 2012). Ten percent of these tumors grow through the intervertebral foramina and look like 'dumbbells' on radiography (Shakoory et al., 2004). If intraspinal expansion has been obtained hence the MRI modality is the best because of its ability to differentiate spinal cord from other soft tissues while detecting spinal cord disorders (Duwe, Sterman, & Musani, 2005). Sakai et al. reported an association between MRI results and pathological features of neurogenic tumors (Sakai, et al. 1992). An image of high intensity and inhomogen in T2 is associated with schwannoma.

Histologically neurofibromas are seen as proliferation of thick and wavy collagen bundles with varying degrees of myxoid degeneration. Neurofibromas are usually homogeneous, have a clear boundary that is the result of irregular proliferation of all nerve elements, including Schwann cells, myelin nerve fibers and non-myelinated nerve fibers, and fibroblasts. On HE staining, you will see areas with hypo and hypercellular joints separated by fibrous stroma and blood vessel branches. Whereas the schwannoma consists of Schwann cells in the background of loose reticular tissue without nerve fibrin or collagen. Schwannomas are often heterogeneous, especially when large, with areas of cystic degeneration, low cellular levels, bleeding, myelin, and small calcifications. Although there are differences from these two nerves, they both manifest as "lobulated spherical masses" (Guo, Chen, & Heffner, 2009). In this case, FNAB CT Guiding examination of the examination revealed distribution and groups of cells with spindle-shaped nuclei, elongated cytoplasm, with fibromixoid mass. On examination of the tissue it was found that the mass was covered with easily released capsules, lobulated outer and inner surfaces. Microscopic examination of tissue consists of the proliferation of spindle nucleated cells until the plump, some navy, fine chromatin, arranged in intersecting fasicles, with histiocyte infiltration. Mitosis is not found. This is consistent with the histological neurofibroma.

Malignant degeneration occurs in 10% of neurofibromatosis, so nerve transection may be indicated for certain patients (Rahman, et al. 2005. Maebeya, et al. 1993). If a large size of mediastinal tumor is found, several things must be evaluated; hypersellularity, the presence of necrosis, the presence of atypical cells expression from Ki-67 and positivity of P53 in immunohistochemistry (Varma, et al. 1992). Unlike a schwannoma which can be excised without damaging the nerves, neurofibroma usually has a more complicated structure and grows diffusely containing all

nerve elements, including axons cells, sheaths, and connective tissue. So it is quite difficult to excise neurofibroma perfectly while maintaining existing nerves (Saito, et al. 2004). If it is related to the phrenic nerve, then unilateral phrenic nerve palsy usually only causes minimal morbidity, but may cause symptoms with limited lung function, assuming the diaphragm works effectively. Schoeller et al. reported that immediate micro reconstruction of the phrenic nerve with graft nerve is less invasive and is quite effective for symptoms of hemidiafragm paralysis.

However, it is recommended that this procedure be carried out if it has sufficient time to allow complete revision, given that the nerves regenerate at a rate of 1-mm per day from the proximal nerve diaphragm, and if the patient's general condition allows the additional time needed for reconstruction without increasing risk. Therefore, in certain patients, phrenic nerve reconstruction is a good method for re-functioning the diaphragm. Because the ultimate goal of surgery is to achieve safe and complete tumor excision, phrenic nerve anastomosis can be performed to prevent nerve paralysis (Schoeller, et al. 2001). Although very rarely neurogenic tumors can grow in the endotracheal, neurilemoma and neurofibroma (Saito, et al. 2004). The majority of neurofibromas occur in the lower third of the trachea, followed by the upper third. In cases like this neurofibroma can be resected with rigid bronchoscopy (Murărescu, et al. 2005). In tumors with intraspinal expansion, the best method is a combination of neurosurgical procedures and thoracic surgery (Shimizu, et al. 2008). If excision of the tumor can be done completely and well, the prognosis of the patient is good (Rahman, et al. 2005).

CONCLUSION

The rare cases of mediastinal neurofibroma without Von Recklinghausen's disease, experienced by female patient aged 59 years. This tumor had reached the stage of surgical therapy to achieve safe and completed tumor excision. This therapy was carried out as an optimal effort to obtain a better prognosis for the patient's disease.

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