

# Course of neurofibromatosis type 1 diagnosed in adult woman

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## Abstract

Neurofibromatosis type 1 (NF1, von Recklinghausen's disease) is one of phacomatoses - genetic disorders triggered by a mutation of a gene. In case of von Recklinghausen's disease the mutation has been recognized as the loss of function mutation of NF1 gene, that results in lack of neurofibromin. The disorder is usually diagnosed in early childhood since some of the symptoms are present in infants or even newborns. In some cases however, the symptoms appear in adulthood only when they might cause diagnostic problems. We present a study of a 32-year old female patient admitted to Pulmonology Department due to a found round mass in her left lung. Further diagnostics revealed other abnormalities and combined with the patient's physical findings the diagnosis of neurofibromatosis type 1 was made. This study presents further medical history of the given patient.

## Introduction

Phacomatoses or neuroectomesodermal dysplasias are developmental changes within tissues that occur as a result of a genetic mutation which leads to growth and cellular differentiation disorders during the period of blastodermic layers and primordia development during the first three to four weeks of intrauterine life. Neurofibromatosis type 1, known also as von Recklinghausen's disease, is the most common of phacomatoses, occurring in 1 in 2,500 to 4,000 individuals in general population. It is inherited as an autosomal dominant trait and caused by a loss of function mutation of the NF1 gene, localized on the long strand of chromosome 17 (17q11.2). Both central and peripheral nervous system are affected but other organs might be affected as well. Diagnosis is usually made in early childhood on the basis of characteristic clinical picture. Sometimes though, the disease stays clinically silent until the adulthood, when it might become diagnostically challenging.

## Case report

In August 2008 a 32-year-old female patient was admitted to Pulmonology Clinic at the University Hospital in Kraków due to a subpleural mass in the lower lobe of her left lung that had been found in a chest X-ray performed because of dyspnea the patient was complaining of. This paroxysmal dyspnea had been occurring for about five to six years, mostly in the patient's workplace - a tannery. A computed tomography of the patient's chest performed for further diagnostics revealed a similar mass in the right lung aside from the previously known one in the left lung. Both of the masses were localized in close adherence to the chest walls and the potential sources of the tumours' origin were established to be intercostal nerves. Furthermore on physical examination multiple skin discolorations of cafe-au-lait sort and tuberous masses on the back - below the left scapula and over the left breast were found and brought to a physician's attention.

The patient stated that in the past she had undergone a surgical excision of skin lesions twice - in 1995 from the left orbital cavity and in 1997 from her left hand. Histopathological picture of the lesions was corresponding to neurofibroma. Besides that the patient had been remaining under neurological treatment due to epilepsy diagnosed in 2001. Electroencephalogram (EEG) revealed then a tendency to paroxysmal discharges. The patient was a non-smoker, consumed alcohol occasionally - a few times a year. Her family history in regard to cancer was positive. Both her father and her mother's brother had died from gastric cancer.

Given the full clinical picture, a preliminary diagnosis of von Recklinghausen's disease was made. Moreover, ophthalmological examination revealed Lisch nodules in both irises. The diagnosis was confirmed by a consultation at genetic outpatient's clinic at Children's University Hospital in Kraków. The patient was referred to surgical ward in order to remove the oval-shaped subcutaneous tumour in her left supraclavicular fossa. The histopathological picture of the tumour was again corresponding to neurofibroma. The tumours in the patient's chest were diagnosed as neurofibromas without further invasive testing due to high probability of that background. Besides that a diagnosis of asthma was made. Because paroxysmal dyspnea occurred only during the patient's work in the tannery the background of asthma was established as occupational having disqualified the patient from hypersensitivity test due to coexisting epilepsy which is a contradiction to consecutive spirometry tests. Asthma was treated with good results. In 2010 the patient stopped her work in the tannery and her symptoms subsided completely.

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In 2009 the mass below the patient's left scapula started to grow. It was then about 6 centimeters in diameter. The patient complained of pain in her left hand. Computed tomography of the chest was performed. The patient was qualified to surgical removal of the mass. Besides that the patient reported periodic neck oedema, most probably connected to a newly revealed in computed tomography mass (22 millimeters in diameter) located in superior mediastinum between subclavian vein and brachiocephalic trunk. Moreover the computed tomography revealed three smooth contoured focal lesions within intercostal spaces: 26 x 33mm at the level of left 9<sup>th</sup> lung segment, 20 x 11mm at the level of right 2<sup>nd</sup> lung segment and 11 x 6mm at the level of apex of the right lung.

In October 2010 the mass below the patient's left scapula (about 11 centimeters in diameter then) was removed and the material was forwarded to histopathological examination that revealed malignant peripheral nerve sheath tumour. After the surgery PET scan was performed that revealed several areas of elevated uptake of the tracer within:

- soft tissues of the back around the left scapula area - corresponding to a postoperative scar;
- a chest wall adjacent nodule of right 2<sup>nd</sup> lung segment of the size of 25 x 12mm;
- a chest wall adjacent tumour of 9<sup>th</sup> left lung segment of the size of 33 x 23mm;
- para aortic lymph nodes of the size of 25 x 33mm in the area of aortic bifurcation;
- a focal lesion of the size of 16 x 14mm within subcutaneous tissue around left iliac crest;
- left internal iliac lymph nodes of the size of 40 x 41mm;
- a tumour within left gluteal area of the size of 64 x 77mm;
- a tumour of the back side of left femur below proximal extremity of the size of 53 x 50mm;
- a tumour within one third proximal of anteromedial part of right femur of the size of 48 x 53mm.

The findings were stated as correspondent to neurofibromatosis type 1.

The patient was referred for further treatment to Oncology Ward at University Hospital in Kraków. Three cycles of chemotherapy (adriamycin in monotherapy) were given from November of 25<sup>th</sup>, 2010 to January of 20<sup>th</sup>, 2011.

In 2011 a relapse of the left scapula tumour occurred. It was surgically removed in April 2011 and identical histopathological picture was confirmed. After the surgery the same schedule of chemotherapy (3 cycles with adriamycin) was administered. Regardless of the treatment a progression of the mass was observed. Radiotherapy of the left scapula area was administered in July 2011. Then another mass in the area of neck was observed. PET scan in September 2011 revealed disseminations of sarcoma. Six cycles of ifosfamide were administered from October 7<sup>th</sup>, 2011 to February 27<sup>th</sup>, 2011 at the Department of Oncology at University Hospital in Kraków. After the treatment PET scan in March 2012 did not show any progression of the disease.

The patient was admitted to Outpatient Ambulatory of Department of Oncology at University Hospital for the last time on April 10<sup>th</sup>, 2012. Her last appointment at Pulmonology Outpatient Clinic at University

Hospital in Kraków took place in May 2012. The patient appeared then significantly changed with masklike face. She complained of progressive weakness, drowsiness, dyspnea for most of the days. Some time later the patient's mother reported the patient's death.

## Discussion

The neurofibromatoses are a group of three different, genetically determined diseases that cause the growth of tumours in the nervous system. Tumours grow in neuroglial cells and myelin sheaths. Neurofibromas develop usually in neurofibromatosis type 1 (von Recklinghausen's disease), while in neurofibromatosis type 2 and schwannomatosis the most often observed type of tumours are schwannomas. Most of the tumours are benign but sometimes they might become malignant. Neurofibromatosis type 1 occur in both sexes and in people of every race and ethnical groups. The diagnosis is most often made in early childhood - almost often by the time a child is 10 years old - as the symptoms are often evident at birth or shortly afterwards. The presented case illustrates an example of the disease's manifest in adulthood.

Many patients inherit the disease, while 30-50% of new cases are caused by a spontaneous mutation in NF1 gene. When the mutation appears, it might be passed to next generations.

Characteristic features of neurofibromatosis type 1 clinical picture are:

- cafe-au-lait spots that usually appear in the first few months of life but might be present in newborns;
- freckling in the area of the armpits or the groins, usually appearing during adolescence;
- subcutaneous nodules - neurinomas or neurofibromas, that appear usually around the age of 10. Neurofibromas might transform to neurofibrosarcomas or malignant peripheral nerve sheath tumours;
- plexiform neurofibromas appearing at every age;
- Lisch nodules - hamartoma type growths on the iris of the eye, found in about 90% of patients above 6 years old;
- bone deformations, pseudoarthroses;
- optic nerve's glioblastomas;
- epilepsy - in 10-15% of children suffering from NF1;
- mental retardation in 20% of patients;
- a common problem is hyperactivity, dyslexia and learning disabilities.

A diagnosis is made in a patient that meets 2 or more of the following criteria:

- five or more cafe-au-lait spots measuring at least 5 millimeters before adolescence or six or more cafe-au-lait stains measuring at least 15 millimeters after the adolescence;
- freckling in the area of the armpits or the groins;
- optic nerve's glioblastoma;
- at least two neurofibromas or one plexiform neurofibroma;
- sphenoid bone dysplasia;
- pseudoarthroses;
- cortical bone deformation;

- two or more Lisch nodules;
- at least one relative with NF1.

Life expectancy in these patients is about 10 years shorter than in general population [1]. Neurofibromatosis type 1 is a progressive disease and, although in some patients the symptoms remain stable, in majority of the patients with the passing time the symptoms escalate. It is impossible to predict the direction of the disease's progression in an individual patient. Neurofibromatosis type 1 increases the risk of cancerous transformation, especially nervous system tumours. Furthermore interstitial lung diseases, lung cancer, pulmonary hypertension and gastrointestinal tract neoplasms might occur - usually in the adulthood [2,3].

Although in general respiratory symptoms are rare in this disease, there are a lot of reports of pulmonary complications of von Recklinghausen's disease. This is the reason why their natural course have not been fully recognized yet, although they might be severe and life-threatening [4,5].

In the illustrated case the mass that primarily seemed to be a lung tumour, turned out to be adjacent to the chest wall and its exact location and the place of origin (intercostal nerve) was established after having chest computed tomography performed. This is how other masses within the chest were revealed as long as costal osteolysis - caused by the biggest of tumours, that corresponds to dural ectasis. [6].

In the presented patient a transformation from neurofibroma to malignant peripheral nerve sheath tumour (MPNST) occurred. Malignant peripheral nerve sheath tumours (MPNST) are aggressive soft tissues sarcomas that take their origin in neural cells. They are characterized by rapid disease progression, high mortality rate, high relapse rate and low response rates to cytotoxic chemotherapy. They

remain amongst the most challenging mesenchymal malignancies to treat. In 50% of cases their occurrence is associated with von Recklinghausen's disease. The prognosis then is poorer than in cases of their spontaneous appearance. In literature reports of higher survival rate in patients with MPNST treated with radiochemotherapy are noticed, which is the treatment administered to the presented patient [7].

In view of wide range of pathological changes arising in the context to neurofibromatosis type 1, further study of individual cases in order to its natural course recognition and treatment methods evaluation is essential.

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