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## Neurofibromatosis type 1 in an adult diagnosed by a pulmonologist

### Abstract

Neurofibromatosis type 1 (NF1), referred to as von Recklinghausen's disease, is a genetic disorder triggered by mutation of the NF1 gene, resulting in a lack of neurofibromin, which leads to abnormalities found in the peripheral nervous system and central nervous system, as well as in other organs. The disease is diagnosed early, usually in childhood by pediatricians. However, in some cases, the disease is clinically silent and remains undiagnosed or is recognized in the late adulthood. We report a case study of a 32-year-old female, who was referred to the pulmonologist with a suspicion of a lung tumor. The patient was admitted to the Pulmonology Department to investigate further the subpleural mass localized in the left lung found by chance in a chest X-ray. Physical examination revealed café-au-lait spots on her skin, several subcutaneous nodules which were confirmed by a histopathology to be consistent with neurofibroma. Further diagnostic testing, such as chest CT, PET and ophthalmological examination, led to diagnosis of neurofibromatosis type 1 with pulmonary involvement.

**Key words:** neurofibromatosis type 1, von Recklinghausen's disease, lung tumor

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### Introduction

Neurofibromatosis type 1 (NF1, von Recklinghausen's disease) is a common genetic disorder that is inherited as an autosomal dominant trait. The disease is caused by mutation of the NF1 gene, which leads to lack of protein neurofibromin. As a consequence, peripheral and central nervous system, as well as other organs are involved. The diagnosis of NF1 is usually made in early childhood by pediatricians. However, in some cases, the disease is clinically silent and remains undiagnosed or is recognized in the late adulthood.

### Case report

A 32-year-old female was admitted to Pulmonology Clinic at the University Hospital in Kraków for further diagnostic testing of subpleural mass in the lower lobe of the left lung. The finding was detected in a chest X-ray (Figure 1), performed because of pa-

roxysmal dyspnea the patient was complaining of for about 5–6 years. The dyspnea occurred usually in her workplace — a tannery.

On admission, the patient was in general good condition, her hemodynamic and respiratory status were stable. Physical examination revealed four café-au-lait macules (measuring 45 × 19 mm, 22 × 8 mm, 48 × 19 mm and 30 × 11 mm), three tumors (25 × 20 mm in the left supraclavicular fossa, 25 × 15 mm over the left breast, and 15 mm in diameter in the right occipital area), and a nodule 10 mm in diameter on her back. Patient manifested the above abnormalities several years prior to the presentation. In 1995 a nodule on palmar surface of her left hand was resected. Histopathological examination was not performed, however. She underwent excision of another nodule from the left suborbital area, which turned out to be neurofibromatous in skin biopsy in 1997. Since 2001 the patient has been treated by neurologist because of her epilepsy. Electroencephalogram (EEG) showed a tendency to paroxysmal discharges. Magnetic reso-

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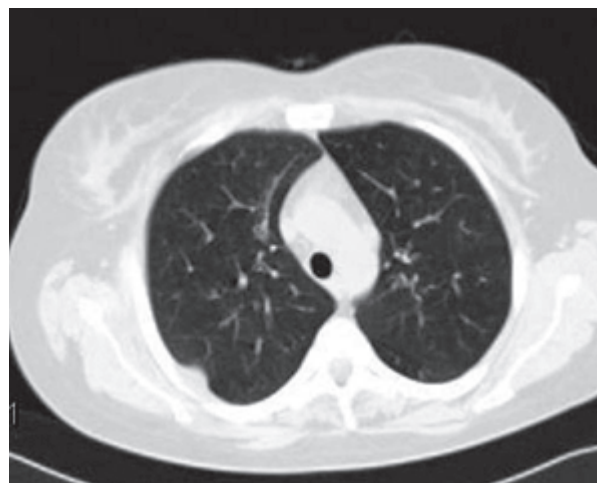
**Figure 1.** Patient's chest radiograph showing two lesions marked and measured



**Figure 2.** Patient's chest CT scanning revealing tumor arising from the left side of the chest wall

nance (MRI) of the brain in 2001 and computed tomography (CT) with contrast in 2008 did not reveal any focal changes. Family history was insignificant.

On subsequent chest X-ray performed in the Pulmonology Department another, smaller nodule in the upper lobe of the right lung was found (Figure 1). CT with contrast demonstrated a  $38 \times 33 \times 24$  mm mass localized on the left side of the thorax in the midaxillary line, in the intercostal space over the costophrenic angle, tightly adjacent to the thoracic wall, accompanied by slight compressive osteolysis of the adherent ribs (Figure 2). Another finding was a mass on the right side of the chest at the level of bifurcation of the trachea, measuring  $19 \times 8$  mm, also directly connected with the thoracic wall (Figure 3). In summary a radiologist stated "diagnostic image of tumorous changes of the chest, which may originate from intercostal nerves". Taking moderate



**Figure 3.** Patient's chest CT scanning revealing smaller tumor arising from the right side of the chest wall

enlargement of the anterior aortal lymph nodes ( $16 \times 12$  mm) into consideration, positron emission tomography (PET) was recommended. However, it did not reveal pathological acquisition of marker in thoracic tumours. The patient was referred to surgery and subsequently underwent removal of the largest skin lesion — an oval, movable nodule in the left supraclavicular fossa. Skin biopsy confirmed neurofibroma. Ophthalmological examination revealed Lisch nodules in both irises. Suspicion of von Recklinghausen's disease was made. The patient was referred to genetic outpatient's clinic at Children's University Hospital in Kraków. Based on patient's history, physical examination (morphology of tumors and cutaneous nodules specific for neurofibromatosis) it was established the patient meets the criteria for NF1. Given the negative family history in respect to neurofibromatosis, it was also determined that disorder was a result of *de novo* mutation. Further observation of the subject was recommended due to variability of the symptoms in NF1.

After 3 months CT of the chest was repeated. No differences in pulmonary findings was noted. Patient complained of dyspnea, nevertheless spirometry was normal. We did not order a hypersensitivity test, due to coexisting epilepsy, which is a contraindication to consecutive spirometry tests. The patient's history revealed that dyspnea occurred only in her workplace (tannery), particularly in rooms with high chemical concentration in air. The patient was referred for an occupational diseases' specialist evaluation with a suspicion of an occupational asthma. She remained under continuous neurologic control. MRI of the brain and medulla was performed periodically.

## Discussion

### Epidemiology and pathogenesis

Neurofibromatosis type 1 is a relatively common (birth incidence 1:2500–1:3000) genetic disease that is inherited as an autosomal dominant trait. It is one of the phakomatoses (Greek *phakoma* meaning *naevus*). The disease often remains undiagnosed, due to its discrete clinical manifestation, different clinical expression even in members of the same family. Phenotypic expression may also be age-dependent.

### Molecular background NF1

NF 1 is a genetically inherited autosomal dominant disease associated with a single NF1 gene mutation. It has been proven to have penetration (probability of disease occurrence in a mutation's carrier) approaching 100% and highly variable expression (that is different clinical manifestation in an affected family as well as between families). NF1 has its own catalogue number (+162200) in a directory of genetic diseases in man (MIM — *Mendelian Inheritance in Man*, also referred to as McKusick catalogue). NF1 gene is localized in 17q1.2 region [1], and encodes protein neurofibromin. A half of new cases is a result of *de novo* mutations and has no hereditary background. Offspring inherits the disease with a typical risk of 50% [2]. Product of NF1 gene, neurofibromin, belongs to the family of proteins that are responsible for GTP-ase activation. It is also an inhibitor of protooncogene *p21ras*. Thus, NF1 gene is a suppressor gene for carcinogenesis [3, 4]. Lack of neurofibromin leads to the development of both benign and malignant tumors, such as: rhabdomyosarcomas, malignant peripheral nerve sheath tumors (MPNST), also known as neurosarcomas (originating from plexiform fibromas) and leukemias.

### Symptoms and diagnosis

The diagnosis of NF 1 is made usually based on physical examination, which includes presence of so-called large (main) and small (additional) symptoms. Large symptoms comprise (in brackets — incidence):

- café-au-lait spots (>99%),
- freckling and hyperpigmentation (70%),
- peripheral fibromas (>99%),
- iris hamartomas (Lisch nodules) with no vision disturbances (>90%).

Small symptoms consist of: macrocephaly (45%) and short stature (30%). In afflicted subjects secondary symptoms and complications may appear, such as: mental retardation (30%), epilepsy (30%), plexiform fibromas that may

undergo malignant transformation (35%). Orthopedic complications (25%) are due to bone dysplasia and deformations, which most commonly cause thoracic scoliosis. Renal artery stenosis is relatively rare (1,5%), may however lead to secondary nephrogenic hypertension. Central nervous system tumors, most often optic nerve gliomas, affect small percentage of patients and typically present early in life. There is 2,5–4 fold higher risk of the above-mentioned malignancy in NF1 patients when compared to general population [5, 6].

Molecular diagnostic testing is not necessary to establish a diagnosis of NF1. In Poland it is routinely inaccessible. Both large and small symptoms tend to vary in a lifetime; therefore prognosis on disease course is impossible.

Obligatory diagnostic criteria of NF1 (*NF1 NIH Consensus Conference Criteria* [7]) were stated in 1997 and sustained in 2007 [8]. Neurofibromatosis type 1 is diagnosed when 2 or more of the following criteria are met:

- six or more café-au-lait spots > 5 mm in diameter prior to puberty or > 15mm post puberty,
- two or more typical neurofibromas of any type or one plexiform neurofibroma,
- freckles/hyperpigmentation spots in areas inaccessible to light (axillary, groin),
- two or more iris hamartomas (Lisch nodules),
- typical bone abnormalities,
- first-degree relative meeting the above criteria.

### Management

Causal treatment is not possible, therefore symptomatic therapy is recommended. Patients require continuous care due to variability of clinical features in life. Patient should also be monitored due to the possibility of malignant transformation of tumours.

### Conclusions

The presented case study is an example of late and accidental diagnosis of NF 1 due to paucity of its symptoms. Developmental disturbances in infancy or signs of the disease that could make the suspicion of NF1 possible were not observed. In adulthood, symptoms most probably unrelated to NF1 (bronchial asthma) contributed to chest X-ray, which subsequently revealed pulmonary masses and led to further diagnostic testing.

Manifestations of NF 1 in chest comprise:

- in lungs:
  - interstitial lung disease (however, it remains controversial whether it truly is associated with NF1) [9, 10],

- metastases of neurosarcomas (generally of a very bad prognosis, despite reports on 5-years' survival after metastasis resection) [11];
- in mediastinum:
  - meningocele,
  - neurofibromas of vagal nerve;
- in thorax wall:
  - subcutaneous neurofibromas,
  - costal dural ectasias due to intercostal neurofibromas compression,
  - kyphoscoliosis,
  - pulmonary apex neurofibromas (Pancoast's syndrome) [12].

In presented case one of the masses, adjacent to the thorax wall, manifested as pulmonary tumor on chest X-ray. Finally, CT visualized precise localization of the change and its relation to neighbouring structures in the chest. It also revealed other findings in the chest wall. Additionally, osteolysis of the ribs due to compression by the largest lesion was noted, which corresponded with dural ectasias described in literature [12]. Taking typical picture of the findings in CT and clinical manifestation as a whole into consideration, we restrained from invasive diagnostic testing. Due to risk of potential neoplastic transformation of the existing neurofibromas, careful observation and regular chest CT were recommended.

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