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Coexistence of neurofibromatosis type 1 with multiple malignant neoplasia

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Abstract

Neurofibromatosis type 1 (NF1, von Recklinghausen disease) is inherited in autosomal dominant way genetic disorder, with an incidence at birth 1:3000. It is one of the most common congenital disorders. It is characterized by café-au-lait spots, neurofibromas, and less common MPTST and gliomas of the optic nerve. It is caused by germline mutations of the *NF1* gene, which acts as tumor suppressor. Inactivation of the gene leads to increased activation of the kinase pathways, and in consequence, uncontrolled proliferation of cells. The disease predisposes to the development of both benign and malignant tumors. Malignant tumors, but not related to the nervous system occur in neurofibromatosis quite rare. The aim of the study is a literature review of NF1, with presentation of a patient with NF1 and coexisting numerous tumors: synchronous somatostatinoma and gastrointestinal stromal tumor with metachronous prostate adenocarcinoma and non-small cell lung carcinoma. And attempt to answer the question if there is a common pathway for oncogenesis of these four tumors.

Abbreviations:

KIT(CD117) and CD 34	- clusters of differentiation markers of stem cells
Cdc42/Rac-PAK1	- p21 protein (Cdc42/Rac)-activated kinase 1
CT	- computed tomography
GIST	- Gastrointestinal stromal tumor
MAP(MAPK)	- mitogen-activated protein kinases
MPNST	- malignant peripheral nerve sheath tumor
MRI	- magnetic resonance imaging
mTOR	- mammalian target of rapamycin kinase
NF1	- neurofibromatosis type 1
NSCLC	- non-small cell lung carcinoma
p21-RAS	- p21 protein activator 1
PDGFRA	- platelet-derived growth factor receptor A
PET/CT	- positron emission tomography combined with computed tomography
PTH	- parathyroid hormone
RAS-MAPK	- The Ras/mitogen activated protein kinase
RET	- receptor tyrosine kinase
TP53	- tumor protein 53

CASE REPORT

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an inherited in an autosomal dominant pattern disease with prevalence 1:4000–1:5000, caused by mutation in tumor suppressor gene *NF1*, located on chromosome 17q11 (Ferner 2007; Friedman *et al.* 1998).

The product of the gene – neurofibromin is a cytoplasmic protein, acting through an inactivation of p21-RAS protein and in an advance – downregulation of kinase pathways – mTOR and MAP, which transduce signals from cell membrane to the nucleus (Brems *et al.* 2009; Gottfried *et al.* 2010). Constant activation of this pathways results in increased proliferation of cells (Brems *et al.* 2009).

NF1 is characterized by flat skin lesions – café-au-lait spots, numerous neurofibromas of the skin, freckling in the axillary and groin area, gliomas of the optic nerve and musculoskeletal lesions. Patients with NF1 have an increased risk of developing benign and malignant tumors (malignant tumors are found in 3–15% of those patients). Life expectancy in patients with NF1 is about 15 years shorter than in general population. The main causes of deaths are malignant tumors (Rasmussen *et al.* 2001; Seminog & Goldacre 2013).

Co-existence of multiple malignancies with NF1 has not been reported much in literature. An example of the occurrence of this type of disorder in a single patient is presented below.

CASE REPORT

In May 2003, 46-year old male patient with diagnosed 15 years before NF1 was admitted to the Clinical Department of Endocrinology at the University Hospital for further diagnosis.

NF1 was diagnosed based on clinical appearance (café-au-lait spots, multiple neurofibromas of skin and spinal canal, Lisch nodules) and positive family history (father and brother of the patient had NF1).

In November 2002 patient was hospitalized in The Department of General, Oncological and Gastroenterological Surgery at the University Hospital because of acute pancreatitis. Computed tomography (CT) and ultrasound of the abdomen revealed pathological mass in the head of the pancreas, with heterogenous echostructure, 45 mm in diameter. In December 2002 patient was again admitted because of cachexia, with symptoms suggesting stenosis of duodenum and tumor of pancreas. He underwent pancreatoduodenectomy with simultaneous cholecystectomy. Histopathological examination of excised tissues revealed ganglioneuromatosis of the mucosa of duodenum, ectopic pancreas with the presence of neuroendocrine tumor cells (positive staining for somatostatin). Within somatostatinoma nodule (15 mm in diameter) there was no mitotic activity. Additionally, on the mucosa of the duodenum there were found 2 nodules, one of which was diagnosed as neurofibroma, and second one (10 mm in diameter) was recognized as gastrointestinal stromal tumor – GIST (positive staining for CD117 protein). During first hospitalization in the Department of Endocrinology patient underwent whole body scintigraphy with somatostatin analogue, ultrasound and scintigraphy of the thyroid gland. Except of small, benign nodules of thyroid (with no clinical significance) there were no pathological findings.

In 2004 laboratory test showed elevated concentration of parathormone (PTH) with hypocalcemia, low Vitamin D and normal phosphate concentration. Repeatedly conducted ^{99}mTc-sestamibi scintigraphy revealed no pathological uptake within parathyroid glands. According to this, secondary to the malabsorption of calcium and vitamin D after pancreatoduodenectomy hyperparathyroidism was diagnosed. In January 2008, another whole-body scintigraphy with somatostatin analogue was performed. It showed only tracer uptake within skin lesions in the lower part of the trunk (in the place of neurofibromas). In June 2009, because of reported recurring short episodes of visual lost, magnetic resonance imagining (MRI) was conducted. It revealed the 16×8 mm extension of the left optic nerve in retrobulbar part suggesting glioma. Moreover, it revealed neuroma of auditory nerve in the proximal part of the right internal acoustic meatus. During the follow-up period the changes remained stable.

In 2010 genetic screening for mutations within protooncogen *RET* and antioncogen *MEN1* was performed – no mutations were found. Because patient met the criteria of the National Institute of Health, no genetic test was conducted to find mutations in *NF1* gene.

In the meantime, due to occurrence of symptoms from gastrointestinal tract (diarrhea, presence of fresh blood in the stool) colonoscopy was performed three times. During the first two, polyps were excised (in 2011 and 2013). In March 2014 CT of abdomen and pelvis showed circular infiltration of the transverse and splenic flexure of the colon. But no pathological changes were seen on the performed colonoscopy in April 2014.

At the same time, in March 2014, patient was diagnosed with adenocarcinoma of prostate (in right lobe – adenocarcinoma Gleason 2+3; in the left lobe – adenocarcinoma, Gleason 3+2).

While qualifying for prostatectomy, imaging studies of the chest revealed a nodular change in the left lung. Extended diagnostics (PET/CT) confirmed the presence of the change in the left lung and revealed a second one, smaller, in the right lung. Based on the examination of the material obtained from a biopsy, a diagnosis of non-small cell lung carcinoma (NSCLC) of the left lung with dissemination to the right lung (carcinoma planoepitheliale nonkeratoticum GI/GII CK 5/6+, p63+, PSA–) was made.

In January 2015, the patient began palliative chemotherapy (navelbine+cisplatin: DDP+NVB). Unfortunately, despite treatment disease progressed. Patient died in May 2015 at the age of 56.

DISCUSSION

The most important question that arises in connection with the case presented, is the question of the relationship between NF1 and tumors, which occurred in the patient described. Besides neurofibromas, NF1 patients are at increased risk of developing benign and malignant tumors. These are mainly tumors derived from neural tissue, such as malignant tumor of the peripheral nerve sheath (MPNST), glioma or astrocytoma (Gottfried *et al.* 2010; Kiuru & Busam 2017; Seminog & Goldacre 2013; Zöller *et al.* 1997).

The frequency of abdominal tumors in patients with NF1 in recent studies varied significantly (5% up to 25% (Basile *et al.* 2010; Cavallaro *et al.* 2010; Fuller&Williams 1991; Heuschkel *et al.* 2001).

GIST is believed to be derived from Cajal interstitial cells (Gopie *et al.* 2018; Sircar *et al.* 1999). Incidence is estimated at around 15–16 cases/million/year. Most of them are found in the stomach and small intestine. The most characteristic is the expression of KIT (CD117) and CD34 proteins (which are used as diagnostic criteria) in those cells. The risk of malignant transformation increases with the size of the tumor and mitotic activity (Miettinen *et al.* 2002). GIST does not give specific symptoms. The most common manifestations are non-specific abdominal pains, symptoms of obstruction or bleeding from the gastrointestinal tract (Andersson *et al.* 2005; Giuly *et al.* 2003).

GIST is the most common neoplasm of the digestive tract in patients with NF1 (up to 25% of patients in autopsy studies) (Ghrist 1963; Zöller *et al.* 1997). In one study, 1.5% of GIST were related to NF1 (Miettinen *et al.* 2006). Higher prevalence of *NF1* gene mutations in GIST patients (up to 50–150-fold increased risk) was shown also in works by Cheng and Andersson independently (Andersson *et al.*2005; Cheng *et al.* 2004). What is more, some authors in their papers stressed the differences between sporadic and NF1-related GISTs (as for NF-1 related GISTs: lack of KIT and PDGFRA mutations, lower mitotic counts, localization in small intestine, presentations as multiple tumors, indolent nature) (Andersson *et al.* 2005; Nishida *et al.* 2016; Wada *et al.* 2016).

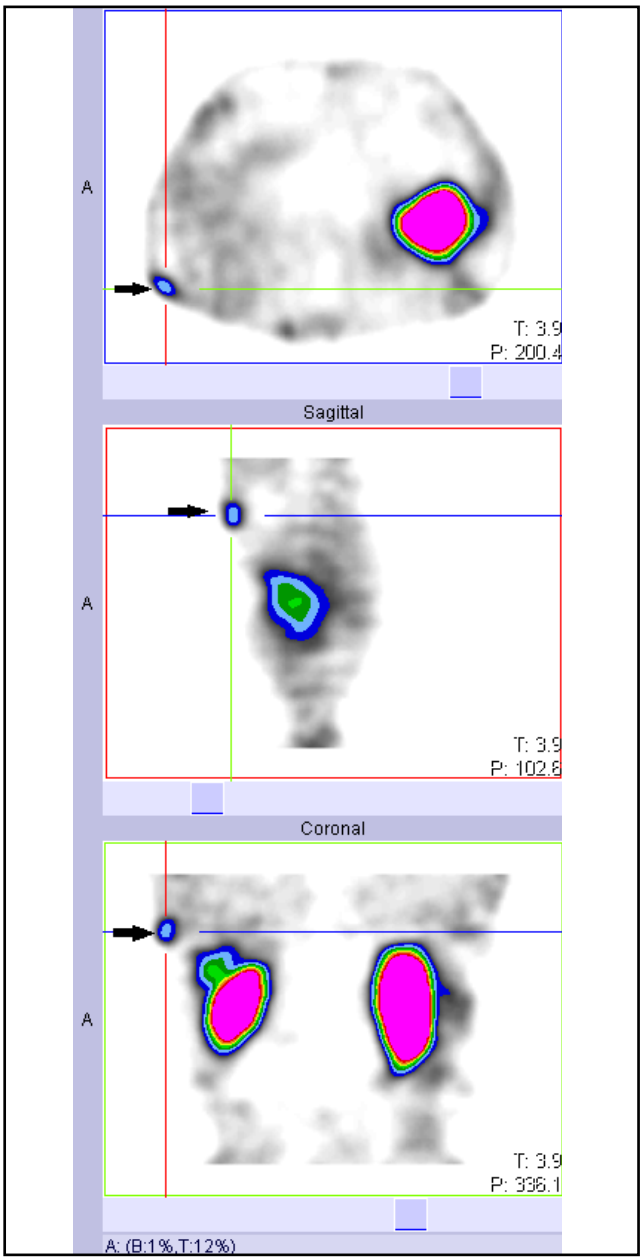

Fig. 1. SPECT images (2008). Tracer uptake within skin lesions in the lower part of the trunk (in the place of neurofibromas).

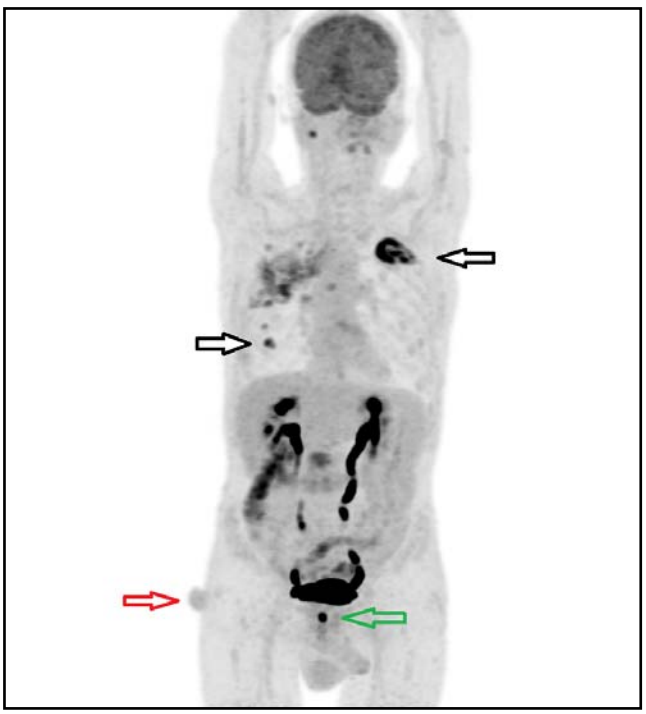

Fig. 2. PET Image (2014). Tumor of the left lung with dissemination to the right lung (black arrows). Neurofibroma of right tigh (red arrow). Metabolically active site in the prostate (green arrow).

The pathogenesis of this nonendocrine tumor in NF1 is not fully known. The hypothesis put forward by Stewart *et al.* indicating the role of loss of heterozygosity in *NF1* gene with the absence of KIT and PDGFRA mutations (as opposed to sporadic GIST) seems to be acceptable. Studies performed by other authors gave similar results (Andersson *et al.* 2005; Kinoshita *et al.* 2003; Steward *et al.* 2007; Yamamoto *et al.* 2009). According to Suzuki *et al.* (2004), the fact that the mutation responsible for NF1 concerns the tumor suppressor gene, increases the risk of nonneuroendocrine malignancies.

There are conflicting reports regarding response to tyrosine kinase inhibitors-imatynib mesylate in NF-1-related GISTs (because of mentioned above absence of KIT and PDGFRA mutations). Some authors (Lee *et al.* 2006) – reported favorable effect, while others (Mussi *et al.* 2008; Nikishita *et al.* 2016) suggested that there was or would be no response to imatynib mesylate.

Somatostatinoma is a rare neuroendocrine tumor with an incidence of 1/40 million/year. However, in patients with NF1 somatostinoma is the most common neuroendocrine tumor, occurring in over 40% of all patients (House *et al.* 2002; Nesi *et al.* 2008; Steward *et al.* 2007; Tanaka *et al.* 2000; Teixeira *et al.* 2016).

Most of these tumors are located in the pancreas (68%), less often in the duodenal papilla of Vater or small intestine. Only in two cases described before year 2009, somatostatinoma was found in ectopic pancreas (Gottfried *et al.* 2010; Miettinen *et al.* 2006).

The literature highlights the frequent occurrence of typical symptoms, in case of somatostatinoma localised in the pancreas (Nesi *et al.* 2008), while less common in other locations, which is confirmed in the present case. Classic triad of somatostatinoma/inhibitory syndrome, manifested by diarrhea, diabetes and cholelithiasis can greatly facilitate the diagnosis. Clinical manifestation of somatostatinoma localised in the duodenum is unspecific and rarely associated with the typical syndrome, which is why this unit is often detected by chance. In paper by Cappelli *et al.* they observed, that NF-1-related somatostatinoma rarely was producing hormones (Capelli *et al.* 2004).

Somatostatinoma is malignant in 60–70% of cases, and the risk of metastasis increases with the diameter of the tumor. The diameter of 2 cm is regarded as cut-off value, above which significantly increases the risk of metastases (Nesi *et al.* 2008; Tanaka *et al.* 2000). In the present case, the diameter of somatostatinoma was 15 mm, and metastases during the entire period of observation of the patient were not observed.

The fact that duodenal tumors are generally smaller, less impact on their malignant potential than their counterparts in the pancreas. By Mao *et al.* (1995), almost 30% of somatostatinoma localised in duodenum and 70% of pancreatic somatostatinoma, metastases occur at the time of diagnosis. This prompts the question of the relationship between the diameter of somatostatinoma occurring in ectopic pancreas in the duodenum and the risk of metastasis. It seems that because they are more similar to the dimensions of duodenal tumors, so they give a better prognosis.

Until recently, it was believed that the simultaneous occurrence of somatostatinoma and GIST is an exceptional and rare case. However, in recent years there have been more and more reports about the coexistence of those tumors in patients with NF1 (Abdessayed *et al.* 2017; Bettini *et al.* 2007; Karatzas *et al.* 2000; Kumar *et al.* 2016; Njei & Sanchez 2014; Rasmussen *et al.* 2001; Relles *et al.* 2010; Suzuki *et al.* 2004; Teixeira *et al.* 2016; Tewari *et al.* 2014; Yamamoto *et al.* 2016). These neoplasms are revealed in older age than skin changes. The presented case of coexistence of somatostatinoma and GIST in a patient with NF1 may constitute evidence of a common genetic path of formation of both tumors on the ground of a mutation. By Barahova-Garrido *et al.* (2009), there is a close link between mesenchymal tumors and neuroendocrine tumors suggesting the existence of a "common path". By Johannessen *et al.* (2008), the following transduction pathways which influence the development of malignant tumors (among them also GIST and somatostatinoma) are taken into account in patients with NF-1: RAS-MAPK, mTOR and Cdc42/Rac-PAK1.

Although lung carcinoma is significantly more common in patients with NF1 (Hsu & Hsu 2015; Kim *et al.* 2012; Seminog & Goldacre 2013; Walker *et al.* 2006), it`s pathogenesis is not fully understood.

One of the proposed theories, is that of the role of a scar tissue in the lung tumorigenesis (Shimizu *et al.* 1994). According to this theory, interstitial fibrosis, and emphysema changes which are seen in patients with NF1 (Casal *et al.* 2018, Reviron-Rabec *et al.* 2016; Ueda *et al.* 2015) are risk factors for lung cancer. Changes in the lung tissue in the course of NF1 would be equal to those observed in cigarette smokers. This has not been finally confirmed (Casal *et al.* 2018; Ryu *et al.* 2005) – the changes have also been reported in non-smoker NF-1 patients. The X-ray and CT of the lungs in our patient reported disseminated fibrosis and numerous emphysema blisters. What is more, patient was for many years a smoker of tobacco and for several years worked in exposure to asbestos.

It is not possible to distinguish changes arising in the course of smoking from those secondary to NF1. Studies by Shimizu *et al.* (1994) and Ryu *et al.* (2005), reported on the development of emphysema changes in younger patients with NF1. The authors suggested that genetic predisposition (*NF1* mutation) in combination with active smoking drove to the earlier development of cancer.

According to the second theory of oncogenesis of lung carcinoma, mutation in a suppressor gene *TP53* (which is also located on chromosome 17 as *NF1* gene) takes participation. Coexistence of inactivating muta-

tions in the gene TP53 and in NF1 was associated with more severe NF1 (Menon *et al.* 1990; Upadhyaya *et al.* 2008). The relation between carcinoma of the lung and inactivation of p53 was revealed previously. Moreover, in smokers compared to non-smokers, there are more frequent mutations in *TP53* (Husgafvel-Pursiainen *et al.* 2000; Takagi *et al.* 1998).

So far only one case has been previously reported of co-occurrence of prostate carcinoma with NF1. Araki *et al.* in 1983 reported the case of 65-year-old patient with NF1, diagnosed with adenocarcinoma of the prostate. Moreover, until recently, no relationship was found between the NF1 and prostate carcinoma as well as between carcinoma of the prostate and other tumors described above. In population-based study, Seminog & Goldacre did not found significantly elevates risks for prostate carcinoma (17 cases observed, expected-23, *p*-value 0.444) (Seminog & Goldacre 2013). Probably changes in RAS/RAF and mTOR signaling pathway, which are observed both in prostate cancers as well as NF1-patients can play a crucial role in the development of both types of cancer. (Stelloo *et al.* 2016; Taylor *et al.* 2010).

It seems likely that the solitary germline mutation in the *NF1* gene is not sufficient to oncogenesis. According to the Knudsons` two hit hypothesis, only in the case of somatic mutation of the second allele of the gene, there is a disclosure of a tumor (Knudson 1971). Perhaps there are a few common pathways for various groups of tumors. Frequent co-occurrence of GIST and somatostatinoma suggests a common pathway. In the case of lung cancer, it appears to be correct the theory on the impact of mutations in tumor suppressor gene TP53. Moreover, the co-existence of the inactivating mutations in the gene of p53 mutations in NF1 was associated with more severe NF1 (Upadhyaya *et al.* 2008) and combined with premature mortality (Rasmussen *et al.* 2001; Seminog & Goldacre 2013).

In literature where mostly presented cases with co-existence of somatinoma and GIST in NF1 patients. Co-existance of more than 2 malignancies is extremely rare. Nevertheless, the NF1 patients with two malignancies should be under strict oncological control.

CONCLUSIONS

1. Patients with NF1 should be under special oncological alertness, as changes in the course of the underlying disease can mask the presence of other neoplastic lesions, including malignant ones.
2. Patients with NF1 who present gastrointestinal symptoms should arouse increased alertness and be observed for duodenum and pancreas tumors.
3. Deeper understanding of genetic and molecular pathways of oncogenesis will allow a better understanding of the pathophysiology of tumors coexisting with NF1 and may give a chance to more effective, targeted treatment.
4. Given the poor prognosis in patients with lung carcinoma, patients with NF1, in particular with changes indicative of fibrosis of the lung tissue, require special careful observation for the emergence of carcinoma.

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