CO-OCCURRENCE OF ADRENOCORTICAL CARCINOMA AND GASTROINTESTINAL STROMAL TUMOR IN A PATIENT WITH NEUROFIBROMATOSIS TYPE 1 AND A HISTORY OF ENDOMETRIAL CANCER

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Abstract

Neurofibromatosis type 1 (NF-1) is an autosomal dominant inherited syndrome affecting 1 per 3000-4000 individuals. Patients with the neurofibromin gene mutation are more likely to develop malignancies. We report the case of a 57-year-old female with NF-1 who presented during her lifetime three neoplasms: endometrial cancer, adrenocortical carcinoma (ACC) and gastrointestinal stromal tumor (GIST). We describe the clinical, radiological and histopathological features of this rare condition. There have been reported only 10 cases of ACC together with NF-1 and 18 cases of ACC with other tumors. To the best of our knowledge it is the first reported case of NF-1 diagnosed with three cancers. Our report indicates the importance of careful and all-embracing care of patients with NF-1 in order to make a thorough investigation of any symptoms that might be a manifestation of a malignant disease.

Keywords: adrenocortical carcinoma, gastrointestinal stromal tumor, ACC, NF1, neurofibromatosis type 1, GIST.

INTRODUCTION

Neurofibromatosis type 1 (NF-1), known as von Recklinghausen disease, is an autosomal dominant inherited syndrome affecting 1 per 3000-4000 individuals (1). The syndrome is caused by a mutation in the NF-1 gene that encodes neurofibromin. NF-1 has one of the highest genetic alteration rates, hence, DNA analysis is not routinely performed, and the diagnosis of NF-1 is based on the presence of two or more major clinical criteria established by the National Institutes of Health (NIH) (2). The classic manifestation of NF1 includes café au lait macules, skinfold freckling, neurofibromas, brain tumors, iris hamartomas, and bone lesions. In addition, patients with NF-1 are at increased risk of mental disabilities,

aqueductal stenosis, pheochromocytoma (PHEO), vascular dysplasia, scoliosis, and cancers, including adrenocortical carcinoma (ACC) (3, 4).

CASE REPORT

A 57-year-old female patient with NF-1 after a hysterectomy in 2011 due to endometrial cancer was admitted to our Department of Endocrinology and Internal Medicine because of a PHEO suspicion. The patient complained of losing 25 kilograms of weight over 9 months, severe post meal abdominal pain, headaches, back pain and poor blood pressure control. Prior to the admission to our hospital, the patient underwent an oncological diagnostic pathway including gastroscopy (gastropathy found), colonoscopy (non diagnostic, patient was unprepared for the examination because of a lack of compliance) and ultrasonography of the abdomen. The latter showed a pathological mass of the left adrenal gland measuring 7-8 cm. Computed tomography (CT) of the abdomen revealed a large well-circumscribed mass of 8.7 x 6.7 x 8.0 cm in the left adrenal gland, with heterogenic contrast enhancement. The tumor contained hypodense areas, likely reflecting necrosis, displaying prominent radiological features of malignancy (Fig. 1). The right adrenal gland was thickened to 15mm with radiological features of a benign nature.

In the patient's family history, her father died due to a brain tumor, and mother due to lung cancer. The younger son of the patient's sister was diagnosed with NF1 and he stays under tight pediatric surveillance. The sister and mother had some NF1 symptoms in the interview. The sister did not agree to our examination in order to confirm the NF1 suspicion. None of the family members underwent genetic testing towards NF1. Our patient meets the clinical criteria for the NF1 diagnosis

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Physical examination at admission showed dark skin pigmentation with many neurofibromas and café au lait spots. No features of virilization or Cushing syndrome were present. Blood pressure was 150/90 mmHg, heart rate 77/minute. The laboratory tests showed lack of diurnal cortisol rhythm. Adrenocorticotrophic hormone (ACTH) concentration, 24 hours urinary free cortisol, androgens, and catecholamine metabolite levels were within the normal range (Table 1). The patient was referred for a left adrenalectomy after prior alpha-blocker treatment. During the laparoscopic adrenalectomy numerous small nodules on the stomach surface, mainly located near to the stomach cardia, were noticed. One of the nodules was removed for further histopathological examination.

Macroscopic examination of the adrenal mass showed a 10.0 x 7.2 cm-sized tumor weighing 358g. Histopathology examination revealed ACC with a diffuse architecture, consisting of oncocytic and myxoid components, with large pleomorphic nuclei. Immunophenotype: melan A (+), inhibin (-), chromogranin A (-), synaptophysin (-), S100 (-). No

Figure 1. Large well circumscribed mass of 8.7 x 6.7 x 8.0 cm in the left adrenal gland.

invasion of vessels or sinusoid was observed. Mitotic rate 18 MF/10 HPF, with multiple atypical mitoses, expanded areas of necrosis and diffuse architecture fulfilled Weiss's criteria for malignancy (Fig. 2). Examination of nodule from stomach displayed GIST, size of 2 mm, mitotic rate 0 MF/ 10 HPF; immunophenotype: CD117(+), DOG1(+/-), CD34(+), S100(-); Miettinen's classification 1st group (very low risk). After re-evaluation of the abdomen CT, a tumor in the horizontal part of duodenum was seen that had not been described by the radiologists in the original report (Fig. 3). The patient underwent a second laparotomy where a 2 cm tumor of duodenum was resected. The histopathology report described a beige tumor sized 2.1 x 1.7 x 1.5cm, GIST ESMO classification group 2, with a very low mitotic rate 1/50 HPF (Fig. 4). Considering the clinical picture, the patient was referred for further oncological treatment.

DISCUSSION

ACC is a rare malignancy with an incidence of 0.7–2.0 cases per million habitants per year. It occurs at any age, with two peak incidences: the first one in the first decade and the second one between 40 and 50 years (5). Women are most frequently affected (55–60%) (6, 7). Most ACCs arise sporadically, however, they can develop as part of the constellation of tumors in inherited familial cancer syndromes. The most commonly reported include Li-Fraumeni Syndrome, Beckwith-Wiedemann Syndrome, Gardner Syndrome, and Multiple Endocrine Neoplasia, type 1. Neurofibromin in adults is expressed mostly in neural tissues and in adrenal medulla and it is impaired expression may result in the development of PHEO (8, 9). Some data has shown that loss of neurofibromin in the adrenal cells may also lead to malignant transformation of adrenal cortex (10). Our case report supports this data to some extent by showing that patients with NF-1 might develop ACC.

Table 1. The patient's hormone profile before and after laparoscopic adrenalectomy

Hormones [reference values]	Before	After
Serum adrenocorticotrophic hormone (ACTH) [<46pg/mL]	24.3	28.5
Serum androstendione [0.3 - 3.5ng/mL]	2.7	1.6
Serum DHEA-S [26-200 µg/dL]	166.0	155.0
Cortisol in 24-hour urine collection [11.8 - 485.6nmol/24h]	462.0	130.9
Morning serum cortisol [nmol/L]	400	265
Evening serum cortisol [nmol/L]	237	110
Metanephrine in 24-hour urine collection [64 - 302 µg/24h]	220	165
Normetanephrine in 24-hour urine collection [162 - 527 µg/24h]	359	277
3-methoxytyramine in 24-hour urine collection [103 - 434 µg/24h]	174	109

Figure 2. Adrenal cortical carcinoma with atypical mitotic figure (A), showing oncocytic (B) and myxoid (C) patterns, both of which were immunoreactive for melan-A (D).

Figure 3. Computer tomography scan shows a duodenal tumor (narrow arrow) and a left adrenal gland tumor (wide arrow).

NF-1 intra-abdominal manifestations varied from 5 to 25% (3). The most common gastrointestinal manifestation of NF-1 is GIST. The mesenchymal tumors in NF-1 patients differ from the sporadic tumors by a lack of GIST-specific mutations such as KIT and PDGFRA. They often are also smaller in size, multiple, with lower mitotic activity, occur in younger patients, and display incomplete response to the tyrosine kinase inhibitor (imatinib) treatment, (1, 11). As described above, the patient had exactly such a histopathological type of GIST.

Figure 4. Spindle cell gastrointestinal stromal tumor (A) with positive expression of CD117 (B), DOG1 (C) and CD34 (D).

The current recommended treatment of ACC is mainly determined by tumor stage, hormonal activity, histopathologic features and markers of proliferation (including mitotic rate and ki67 expression). The treatment basically consists of surgical resection (complete resection is possible for stages I-II and usually for III, and it is the only potentially curative treatment) and adjuvant mitotane therapy. Open resection is recommended, especially for tumors more than 6 cm in size and all tumors where radiologic findings show evidence of local invasion. For the ACC histologic diagnosis a Weiss scoring system is widely accepted. It

is based on nine histopathologic features (nuclear grade, mitotic rate, atypical mitoses, clear cell component, diffuse architecture, tumor necrosis, invasion of venous or sinus structures, or tumor capsule). The presence of more than three features is considered as ACC. All patients after surgery should receive mitotane. The Ki67 labeling index (LI) > 20 percent might be used to select patients for adjuvant cisplatin chemotherapy in addition to mitotane. The other post surgical options are radiation or radiofrequency ablation (12).

The surgical GIST resection is the treatment of choice for potentially resectable tumors, however initial

Table 2. Adrenocortical carcinoma reported in patients with NF-1

No.	Publication	Case
1	Fraumeni & Miller, 1967 (16)	4.5-yo girl with NF1, ACC with brain metastasis. 16- and 17-yo girls of ACC associated with <i>café au lait</i> spots
2	Fienman & Yakovac, 1970 (17)	One case of NF1 and ACC with a thalamic tumor
3	Sorensen <i>et al.</i> , 1986 (18)	46-yo female with NF1, ACC and reticulosarcoma, one more case NF1 and ACC with no further details about the case
4	Gutmann <i>et al.</i> , 1994 (19)	One case of NF1 and ACC
5	Wagner <i>et al.</i> , 2005 (20)	3-yo girl with NF1 and ACC and paraspinal metastasis
6	Menon <i>et al.</i> , 2014 (10)	49-yo female with NF1 and ACC
7	Minkiewicz <i>et al.</i> , 2020	57-yo female with NF1, ACC and GIST

Table 3. Tumors diagnosed in patients with adrenocortical carcinoma (ACC)

No.	Publication	Patient Age/sex	ACC localization	Tumor(s)/ disorders	ACC stage
1	Eisinger <i>et al.</i> , 1995 (21)	NA	NA	Breast and rectal adenocarcinoma (familial polyposis)	NA
2	Inoue <i>et al.</i> , 1998 (22)	M/ 57 yo	Left	Stage IIIB testicular seminoma	II
3	Pivnick <i>et al.</i> , 1998 (23)	18 m	Right	Ganglioneuroblastoma (Turner syndrome and germline p53 mutation)	IV- lung metastases
4	Khayat <i>et al.</i> , 2004 (24)	M/ 7 yo	NA	Osteosarcoma and rhabdomyosarcoma (germline p53 mutation)	IV- kidney invasion
5	Lorusso <i>et al.</i> , 2004 (25)	M	NA	Lung carcinoma	II
6	Noordzij <i>et al.</i> , 2007 (26)	F/ 64 yo	NA	Papillary thyroid carcinoma	IV- liver metastases
7	Jani <i>et al.</i> , 2008 (27)	M/ 53 yo	Left	Renal cell carcinoma	III
8	Guerrero <i>et al.</i> , 2010 (14)	F/ 32 yo	Left	Ovarian and endometrial adenocarcinoma	II
9	Majhi <i>et al.</i> , 2011 (28)	F/ 27 yo	Left	Renal cell carcinoma	II
10	Wanta <i>et al.</i> , 2011 (29)	M/ 31 yo	Left	Papillary thyroid carcinoma	II
11	Lo Monte <i>et al.</i> , 2011 (30)	F/ 37 yo	NA	Papillary thyroid carcinoma (79m after renal transplantation)	II
12	He <i>et al.</i> , 2013 (31)	F/ 12 yo	Left	Left ovarian teratoma (46 XX karyotype)	IV- lung metastases
13	Karakose <i>et al.</i> , 2013 (32)	M/ 40 yo	Left	Papillary thyroid carcinoma	II
14	Courtney <i>et al.</i> , 2014 (33)	Infant	NA	Paraspinal neuroblastoma (I162F p53 gene mutation)	NA
15	Kovecsi <i>et al.</i> , 2015 (15)	M/ 71 yo	Right	GIST- stomach	IV- gastric metastases
16	Patodia <i>et al.</i> , 2015 (34)	F/ 55 yo	Right	Clear cell renal cell carcinoma	II
17	He <i>et al.</i> , 2018 (35)	F/ 29 yo	Left	Ovarian malignant mixed germ cell tumor	NA
18	Minkiewicz <i>et al.</i> 2020	F/ 57 yo	Left	GIST- duodenum with metastases to stomach (NF-1)	II

therapy with Imatinib may be preferred. All GIST more than 2 cm in size should be resected. Adjuvant Imatinib treatment is recommended for completely resected GISTs more than 3 cm in size (13).

The last patient's CT scanning of the chest, abdomen and pelvis was performed 6 months after the last surgery and showed no features of recurrence or metastases.

After the ACC surgery, our patient should receive the adjuvant mitotane therapy, but due to poor compliance she was not exposed to this treatment. GIST at this moment stays under radiological and

clinical control.

The risk of developing synchronous ACC with other malignant tumors is extremely rare (14). The first case in the literature of synchronous ACC and GIST was reported in 2015 (15). We present the first case of co-occurrence of ACC with GIST in a patient with NF-1 who also had a history of endometrial cancer. There have been reported only 10 cases of ACC together with NF-1 and 18 cases of ACC with other tumors (Tables 2 and 3). There have been no reports of NF-1 patients diagnosed with three cancers. Our report points out the importance of careful and all-embracing

care of patients, especially with any familial cancer susceptibility syndromes or genetic disorders in order to make a thorough investigation of any of symptoms that might suggest a malignant disease.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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