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Case Reports

Metastatic ovarian cancer and gastrointestinal stromal tumor on the grounds of neurofibromatosis. A case report and review of the literature

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Summary

Neurofibromatosis type 1 (NF1) is an inherited neurocutaneous syndrome. NF1 patients are at increased risk for both benign and malignant tumors. The authors present the case of a female patient with a medical history of NF1, with an impressive succession of tumors, namely metastatic ovarian cancer and, 20 years later, a gastrointestinal stromal tumor (GIST) of the jejunum. The metastatic ovarian Müllerian adenosarcoma was successfully treated with total abdominal hysterectomy with bilateral salpingo-oophorectomy, radiotherapy, chemotherapy, as well as Gamma Knife radiosurgery of the metastasis in the thalamus. The jejunal GIST was surgically removed. The exploration of molecular pathways that underlie the association between NF1, GISTs, and ovarian cancer may provide valuable insight into the pathogenesis of such cases and assessment of targeted therapies.

Key words: Neurofibromatosis type 1; Ovarian cancer; Gastrointestinal stromal tumor; Metastasis.

Introduction

Neurofibromatosis type 1 (NF1) is a neurocutaneous syndrome, which is inherited either in an autosomal dominant manner or sporadically in nearly half the patients [1]. The first time the disease had been described was by a German doctor, named Friedrich von Recklinghausen, in 1882 [2]. The frequency of this disease is about one out of 3,000 births [3]. The principal manifestations of NF1 are café-au-lait spots, congenital pseudarthrosis of the tibia, and Lisch nodules [4].

Life expectancy of patients is reduced by approximately ten to 15 years, with the main cause of death being cancer [5]. The NF1 gene is a gene located on chromosome 17q11.2. It encodes neurofibromin, a protein, known to be a tumour suppressor. NF1 patients are at high risk of carcinogenesis, as an inactivation of the gene leads to loss of regulation and growth of many types of malignancies [6]. Patients are at increased risk for both benign and malignant tumors, compared with the general population; some of the most frequent tumors are optic gliomas, plexiform neurofibromas, and pheochromocytomas [7].

The authors present the case of a female patient with a medical history of NF1, with an impressive succession of tumors, namely metastatic ovarian cancer and, 20 years later, a gastrointestinal stromal tumor (GIST) of the small intestine.

Case Report

The patient was diagnosed with NF1 at the age of 35. In November 1994, at the age of 46, the patient was suspected to have ovarian cancer as raised by the clinical and ultrasound examination. She underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy due to a 12×9×9 cm tumour in the left ovary. Histopathological examination revealed a Müllerian adenosarcoma, which developed on an environment with endometriosis, with a low-grade stromal component. The Müllerian adenosarcoma is a low-grade tumour; heterologous elements were not observed. The epithelial elements were uniformly organized in the stroma without sarcomatous overgrowth. The patient was subsequently subjected to radiotherapy and chemotherapy. A year later, in November 1995, she suffered epileptic seizures and a tumor in the left thalamus was revealed by the MRI examination. The tumor was treated with Gamma Knife radiosurgery in a single session with a prescribed 25 Gy dose on November 30, 1995. A follow-up visit carried out on January 18, 1996, indicated diminished volume of the tumour, which continued to decrease until June 19, 1996. In September 1996, however, there was a slight (15-20%) increase in volume. A complementary FDG-PET scan in February 1997 verified the suspicion of tumor recurrence, the volume of which was three cm^3.

The patient was then retreated with Gamma Knife radiosurgery with the thalamic metastasis being treated with a prescribed 20 Gy dose and a maximum 44 Gy dose on February 20, 1997. Further follow-up visits were uncomplicated and the most recent MRI carried out on March 20, 2015, 18 years after retreatment, did not indicate any evidence of persisting brain metastasis or new tumors.

In February 2003, the patient mentioned smelly vaginal dis-

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charge. Thus, pelvic exam and test Pap were performed. The cytologic examination showed atrophic vaginitis without evidence of malignancy and it was recommended that she repeat the test a year later (2004). Further follow-up visits did not add any new information to the initial diagnosis. Additionally, a mammography was recommended in November 2004. So far, no suspicious abnormalities or malignant tumors have been detected through gynaecological examinations and mammographies.

In June 2013, during the clinical examination, a large postoperative midline hernia was diagnosed. During the medical checkup in order to repair the hernia, a heterogeneous mass which measured 3.5 to 4 cm was found above the urinary bladder in the ultrasound examination. This finding was confirmed by a new ultrasound and CT in May 2014. The tumour markers (CEA, Ca-125, Ca19-9, aFP) were negative and another CT or MRI was suggested to be carried out after three months. However, in June 2014, the 66-year-old patient underwent a new MRI of the upper and low abdomen and a 32-mm solid mass, which may have been due to a neurofibroma or GIST, was revealed in the minor pelvis. In July 2014, it was surgically removed, without complications. A very low-grade jejunal GIST was diagnosed in the histopathological examination. Immunohistochemical examination defined cells, positive for CD117, CD34 a-SMA, negative for S-100, and desmin and one to three mitoses per 50 high-power fields. Written informed consent was obtained by the patient for the publication of this case report.

Discussion

This case report is characterized by a striking succession of tumors on the grounds of NF1, namely metastatic ovarian cancer and, 20 years later, a GIST in the small intestine. A correlation between NF1 and GISTs has been reported [8]. The incidence of GIST in NF1 patients is 3.9−25% [3]. In NF1 patients, there are other mutations than KIT or PDGFRA, which means that the pathogenesis of GIST is divergent [9]. Specifically, the deactivation of neurofibromin is a mechanism to hyperactivate the MAPK pathway; the PI3K-AKT pathway is less activated in GISTs related to NF1 in comparison with sporadic GISTs [10].

There is a limited list of therapeutic choices in NF1 with GISTs. So far, management of GIST in those patients is considered to be surgical removal. The use of imatinib, which is a tyrosine kinase inhibitor, as adjuvant treatment, is not recommended since there is evidence of poor response to this therapy. Nonetheless, it could be useful for patients with metastatic disease [3,11].

Little information exists about the occurrence of ovarian cancer on the grounds of NF1; benign ovarian tumors have been reported in NF1 patients, including neurofibromas [12, 13] or ovarian serous cystoadenofibromas [14]. To the present authors' knowledge, this is the first time a Müllerian adenosarcoma has been reported on the grounds of NF1. Müllerian adenosarcomas are identified by a benign, but sometimes atypical, epithelial, and a malignant, usually low grade, stromal component [15]; immunohistochemically, CD10 is the most common positive marker. Estrogen and progesterone receptors are also often expressed [16]. The most usual amplification implicated MDM2 and CDK4. Some Müllerian adenosarcomas have mutations of pathways reported in endometrial adenocarcinoma, such as the PIK3–AKT/PTEN pathway, while TP53 mutations have been reported [17].

Neurofibromin activates ras GTPase, which catalyzes the hydrolysis of ras-GTP (active form) to ras-GDP (inactive form). Reduction or loss of the protein triggers ras-related signaling pathway, which modulates other pathways, including mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR) kinase, and phosphatidylinositol 3-kinase (PI3K) [3]. Induction of these pathways contributes to cell proliferation and survival. Due to hyperactivation of RAS, NF1 is a tumor predisposition syndrome, classified as a RASopathy [2]. Although the neurofibromin–RAS–MAPK pathway is critical for intermediating NF1-mutant tumor growth [18], other cascades of downstream signaling pathways are probably involved. A potential solution was the use of farnesyl transferase inhibitors targeting RAS-signaling pathway, but clinical trials on these agents showed no tumor reduction. Moreover, increasing proteotoxic stress combined with rapamycin therapy induced tumor remission in genetically engineered mouse models [18,19].

The RAS/RAF/MEK/ERK pathway transfers signals from the membrane receptors to the nucleus. Many compounds can inhibit steps in the MAP/ERK pathway, and, therefore, are potential drugs for treating cancer, such as Raf inhibitors and MEK inhibitors. Selumetinib, an MEK inhibitor was tested in mouse models and has shown positive results [20]. This significant response to MEK inhibition led to clinical trials for patients with NF1 and the results are more than promising [21].

Although neurofibromin has been extensively studied, many functions and possible interactions remain unknown; a significant target of the following years will be to interpret non-RAS–signaling pathways [18]. The exploration of molecular pathways that underlie the association between NF1, GISTs, and ovarian cancer may provide valuable insight into the pathogenesis of such cases and assessment of targeted therapies.

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