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Management of the Case of a Young Female Patient with Multiple Malignancies and Germline R24P CDKN2A Gene Mutation

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ABSTRACT

The case of a young female patient with metachronous primary melanomas, advanced breast and pancreatic cancers is reported. The 5 different tumors diagnosed within six years, were managed with curative intent. Genetic analysis revealed the mutation of the R24P CDKN2A gene in a heterozygote form in both the patient and her father. Careful tertiary prevention during the follow-up of the patient is needed.

Keywords: Breast Cancer; Melanoma; Pancreatic Cancer; R24P CDKN2A Gene Mutation

1. Introduction

The prevalence of multiple primary malignancies varies between 0.73% - 11.7% [1,2]. The synchronous occurrence of primary malignancies is uncommon, but metachronous primary tumors are diagnosed more frequently due to the longer survival of the population and the successful therapy of malignancies [3]. Depending on the time between the diagnosis of the individual malignancy, multiple primary malignancies can be divided into two categories. Synchronous cancers occur within 6 months, whereas metachronous multiple malignancies occur later than 6 months after the diagnosis of the first malignancy [4]. In cases with multiple malignant diseases manifested at a young age, the possibility of genetic predisposing factors responsible for the elevated cancer risk is considered. The history of different cancers among the family members may further support the suspicion of the presence of inherited gene mutation. The detection of five different primary tumors within six years is quite rare. Here we report the case history of a young female patient with successfully treated malignant melanomas, breast and pancreatic cancers.

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2. Case Report

In December 2006, a 1.5 cm malignant melanoma was removed from the left waist region of a 31-year-old Caucasian female patient. From the left inguinal region one, from the left axillary fossa four sentinel lymph nodes were excised, that proved metastasis-free at histological examination. Because of the stage pT2b, Clark II-III pN0 (sn), a one-year adjuvant low-dose interferon-alpha therapy was given.

At a routine follow-up examination, in February 2008, a 2 cm mass in the left axillary region was found, and removed. Histological analysis showed a lymph node infiltrated with anaplastic breast carcinoma, ER, PR and HER2 negative. Imaging examinations were carried out. Breast MRI showed multiple small foci with contrast medium enhancement in the left breast parenchyma, and a 13 mm lymph node in the ipsilateral axillary fossa. Abdominal-pelvic CT showed the widening of the head of the pancreas. On PET/CT, a 1 cm FDG accumulation at the upper quadrants of the left breast and a 7 mm FDG-avid lymph node in the left axillary fossa were apparent. At the border of the body and tail of pancreas, another 1.5 cm FDG-avid lesion was visible (**Figure 1**).

First, left mastectomy and axillary lymph node dissec-

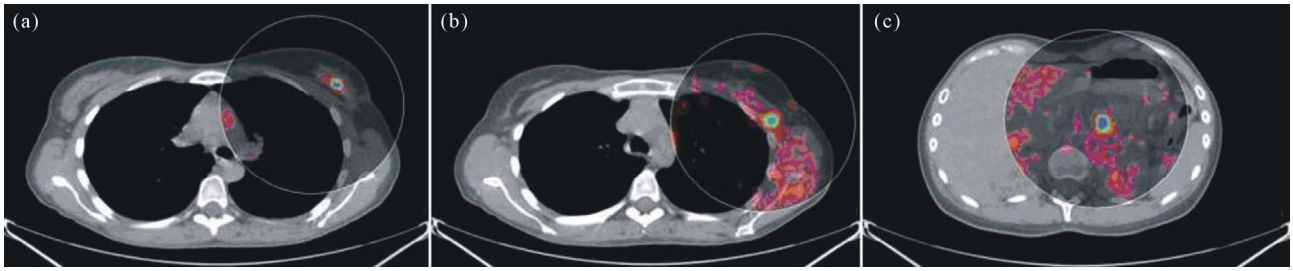

Figure 1. PET/CT scans illustrating (a), the malignant tumor of the left breast (b), with axillary lymph node metastases, and (c), a 1.5 cm FDG-avid lesion at the border of the body and tail of the pancreas.

tion were carried out. Histology revealed multifocal invasive ductal cancer of grade III, pT1 (12 mm), lymphovascular invasion, pN1 (2/14), ER: negative, PR: 60% positive, HER2: negative. Next, the abdominal status was further investigated. At abdominal MRI a 2 cm mass in the tail of the pancreas, at ERCP, the blockade of the pancreatic duct at the border of the body and the tail were apparent. Explorative laparotomy was carried out with liver and lymph node biopsies that revealed the metastatic involvement of these organs by pancreatic adenocarcinoma. Combination chemotherapy of gemcitabine-cisplatin was considered as appropriate both as adjuvant chemotherapy for the breast cancer and neoadjuvant/palliative therapy for the pancreatic cancer. Six cycles were delivered with antiemetics, granulocyte colony stimulating factor and erythropoietin therapy, and meanwhile thoracic, abdominal and pelvic CT examinations, and serial determinations of the tumor marker CA 19-9 were carried out. All studies indicated continuous tumor regression, and the disappearance of the pancreatic tumor after the completion of the chemotherapy. A second PET/CT indicated complete tumor regression, therefore a second abdominal surgery was suggested. In May 2009, the resection of the pancreatic tail with splenectomy was carried out. Profound histological evaluation indicated no tumor tissue in the specimen, nonetheless, the presence of chronic fibrous and inflammatory changes. Since that time, the patient, until recently, was tumor-free and has experienced no longterm complication of the therapies. Three months ago, at routine follow-up examinations, 2 superficial melanoma-suspicious skin lesions were detected on the right arm and the abdominal wall. The excision of these lesion, indicated pTa and pTb melanomas, respectively, excised in toto. No sentinel lymph node biopsy was carried out.

Since the patient reported multiple cancer cases in her father's family (her father suffered from laryngeal and gastric carcinoma, her aunt deceased due to breast cancer at a young age), genetic tests were carried out as described previously [5]. Genetic analysis revealed that both the patient and her father carried a R24P CDKN2A germline mutation in a heterozygote form. At the same time, the presence of hotspot BRCA1 and BRCA2 mutations was excluded by sequencing [5].

3. Discussion

We report here a rare case of young female patient with multiple cancers. Genetic testing revealed a heterozygotic germline mutation of the CDKN2A gene as background of the patient's increased cancer risk. The management of each malignancy was carried out with curative intent, despite the presence or the history of other malignancies. Heightened attention and awareness are necessary for the prevention and early detection of possible additional metachronous malignancies during the follow-up of the patient. Efforts are made for the rehabilitation of the patient.

The relatively young age of the patient and the occurrence of multiple primary malignancies raised the possibility of inherited gene mutation as predisposing genetic factor that was strengthened by the family history. The genetic profiling of the patient and her parents was carried out. No BRCA1 or BRCA2 mutations were detected, however, the mutation of the CDKN2A gene [6-8] was verified in the patient and her father as described in detail previously [5]. The CDKN2A gene located on chromosome 9p21 has been identified as a susceptibility gene for familial melanoma and less frequently for pancreatic cancer [7-11]. The combination of melanoma and pancreatic cancer or melanoma and breast cancer, have been reported in CDKN2A gene mutation carriers as rare events [6-8]. Our patient showed very high susceptibility to melanoma by developing multiple primary melanomas, and developed also pancreatic and breast cancers. The products of this gene play a role in cell arrest in the G1 phase and induce apoptosis [7]. The altered function of this tumor suppressor gene very likely played a role in the development of the patient's synchronous and metachronous tumors and represents a permanent risk factor for further malignancies. Thus, the careful follow-up of the patient and the family members is essential.

The need of the simultaneous management of the synchronous breast and pancreatic cancers raised the question what could be the optimal oncological therapy in this

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case with locally advanced pancreatic cancer and liver metastases of limited extent, and high risk breast cancer. A polychemotherapy regimen found active both in pancreatic cancer [12] and breast cancer [13,14] was selected as neoadjuvant chemotherapy for the pancreatic cancer and as adjuvant chemotherapy for the breast tumor. We speculate that the role of the inherited gene mutation can not be excluded in the unexpectedly good response of the advanced pancreatic and breast cancers to chemotherapy.

Although the metastatic spread to the pancreas or the breast are rare events [15,16], this possibility must have been taken into consideration during the management of the case. The diagnosis of each primary malignancy was carefully obtained using various imaging and pathological methods as described in detail previously [5]. Each malignancy was managed according to its actual stage and pathological features.

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