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Melanoma-Predisposing CDKN2A Mutations in Association with Breast Cancer: A Case-Study and Review of the Literature

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1. Introduction

The authors present the case of a 33-year-old female patient who developed melanoma, ductal adenocarcinoma of the breast and primary pancreas adenocarcinoma nearly simultaneously, but independently of each other. Past medical history of the patient was unremarkable, however, in her family history gastric, laryngeal and breast cancer was noted on the paternal side. The occurrence of multiple primary tumours in a relatively young individual, together with the family history of different malignancies, suggested that there might be genetic predisposition to the development of multiple tumours. In this chapter we present the case of the young female patient suffering from three independent primary tumours and review current data on the germ-line mutations detected to date in the CDKN2A gene, in view of the association not only with melanoma, but also with additional malignant diseases, such as pancreas carcinoma and breast cancer.

2. Case presentation and review of the literature

2.1 Clinical observations and management

The 33-year-old female patient presented with a lesion which had the clinical appearance of a verrucous pigmented nevus on the left lower back for the preceeding 2 years. Histology of the excised lesion showed a pT2b stage malignant melanoma consisting of exulcerated nodular (Fig. 1a) and superficial (Fig. 1b) areas with 1.524 mm Breslow's thickness and Clark's level II-III. Based on the above results, reexcision and sentinel lymph node biopsy were performed. Histological examination of the sentinel lymph nodes from the left axillary

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and left inguinal regions did not reveal any metastases. Staging investigations – chest x-ray, ultrasound scan of the abdomen, pelvis, left axillary and left inguinal regions – did not find any regional lymph node or internal organ involvement. Results of laboratory tests, including serum lactate dehydrogenase levels, were all normal. The patient received low dose (3 MIU – 3 times a week sc.) interferon-α 2a treatment for one year.

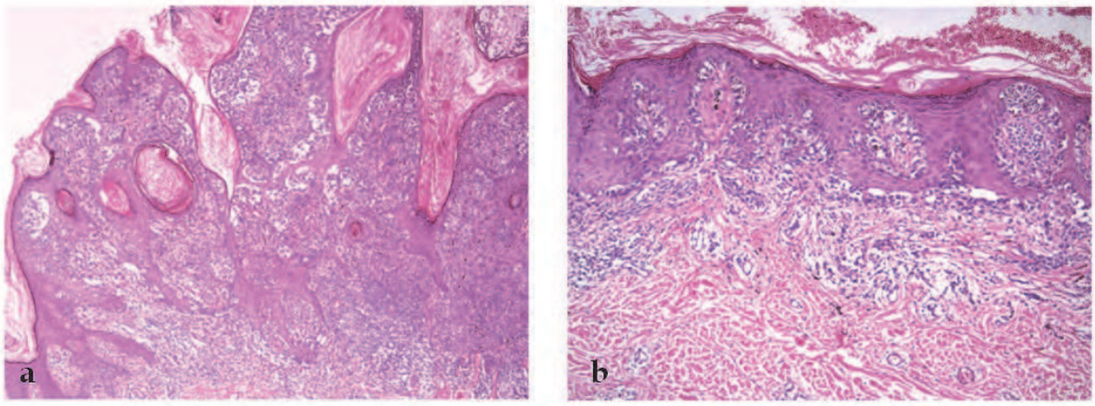

Fig. 1. Histology of primary malignant melanoma. Hematoxylin-eosin staining of the excised lesion revealed its combined nature having nodular (a) and superficial (b) parts.

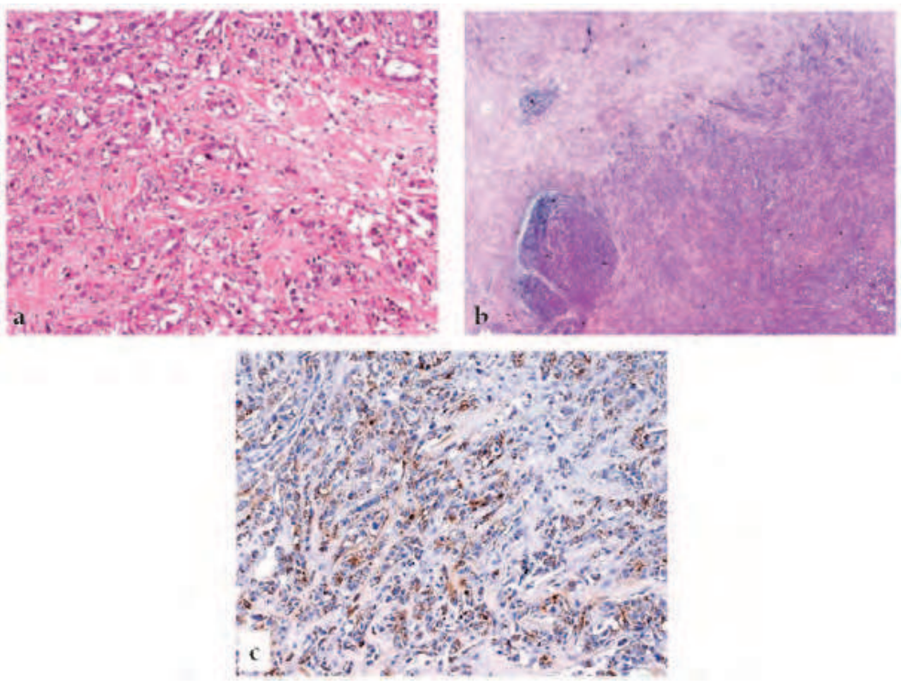

Fig. 2. Histology and immunohistochemistry of the breast adenocarcinoma. The marked nuclear polymorphism, lack of tubular forming and high number of mitoses indicated the diagnosis of ductal adenocarcinoma (a). Two of the excised 14 lymph nodes proved to have metastases with capsular invasion (b). HMF-G staining indicated a poorly differentiated breast adenocarcinoma (c).

Fifteen months after the completion of interferon treatment, the patient noted a firm nodule in the lateral area of the left breast which was biopsied. Histological examination revealed four foci of Grade III invasive ductal adenocarcinoma (Fig. 2a). Grading was based on the marked nuclear polymorphism, lack of tubular forming and high number of mitoses. In view of the multifocal malignant enhancement seen on the MRI and the histology report of the core biopsy, the patient underwent left mastectomy with radical left axillary lymph node dissection. Metastases infiltrating the capsule were found in 2 out of the 14 lymph nodes examined (Fig. 2b).

With regards to the diagnosis of breast cancer, PET CT was performed in order to exclude dissemination. The PET CT suggested the presence of a malignant lesion in the region of the pancreas. Abdominal MRI revealed a neoplasm of 2 cm in diameter in the caudal part of the pancreas (Fig. 3a). Laboratory investigations showed elevated CA 19-9 and serum amylase levels. On explorative laparotomy, an irresectable tumour mass involving the pancreas, liver and the regional lymph nodes was found. The tumour was biopsied and was initially described as metastatic adenocarcinoma (Fig. 3b). However, further immunohistochemical (CK20 and CK7) and mucin staining (MUC5AC) of the specimens from the breast (Fig. 2c) and abdominal mass (Fig. 3c), clearly differentiated two tumours: 1. poorly differentiated [CK7+/CK20-/MUC5AC-] breast adenocarcinoma, 2. moderately differentiated [CK7+/CK20+/MUC5AC+]) pancreas adenocarcinoma. This verified the gastrointestinal origin of the primary tumour i.e. the abdominal mass originated from the primary pancreas adenocarcinoma.

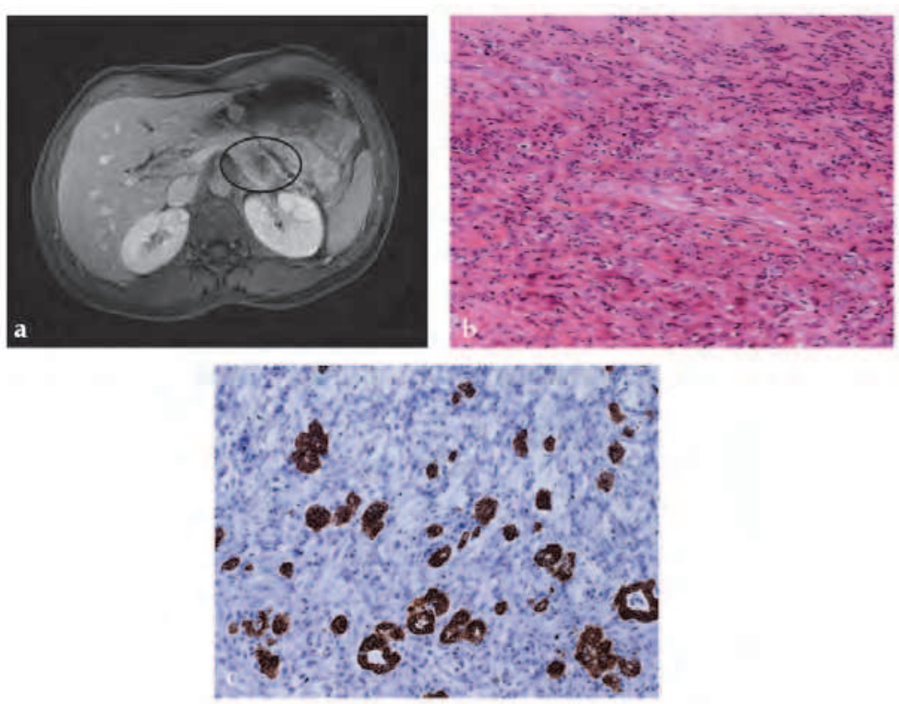

Fig. 3. Diagnosis of pancreas adenocarcinoma. Abdominal MRI showed a neoplasm in the caudal part of the pancreas (a). Hematoxylin-eosin staining indicated the malignant nature of the excised tumour (b). CK-20 immunohistochemistry indicated a moderately differentiated metastatic adenocarcinoma with globular components in the pancreas (c).

With regards to the case of multiple primary tumours, the patient received gemcitabine plus cisplatin combined chemotherapy. Repeated laparotomy performed on follow up after the treatment course noted complete regression of the previously detected primary tumours and tumour-free abdominal organs. Subsequently, the results of all re-staging investigations were negative and tumour markers returned to the normal range.

2.2 Genetic investigations

During the course of the patient's treatment, her family history for tumours was investigated. She reported that her father was suffering from gastric and laryngeal carcinoma and that her father's sister had died from breast cancer at a young age several decades ago. (Fig. 4a). We therefore set out to perform genetic investigations and check whether there are any cancer predisposing factors, causing the high prevalence of simultaneously appearing independent primary malignancies in the patient and in her family. The blood samples used in this study were taken after written informed consent of the patient and family members. The protocol was approved by the Local Ethics Committee in adherence to the Helsinki guidelines. Two ml of venous blood was taken, genomic DNA was isolated using the QIAmp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and exons 1α, 1β, 2 and 3 of the CDKN2A gene were amplified with the Resequencing Amplicon probe system (http://www.ncbi.nlm.nih.gov/genome/probe/reports/probereport; probe IDs: RSA001284450, RSA000045423, RSA000942236, RSA000942233). The PCR products were purified using the Quantum Prep PCR Kleen Spin Columns (Bio-Rad, Hercules, CA, USA). The genetic analysis revealed that the patient and her father both carried the R24P CDKN2A mutation in a heterozygote form (Fig. 4b). The mutation is located in exon 1a, therefore only the $p16^{INK4a}$ transcript variant is affected (Fig. 4c).

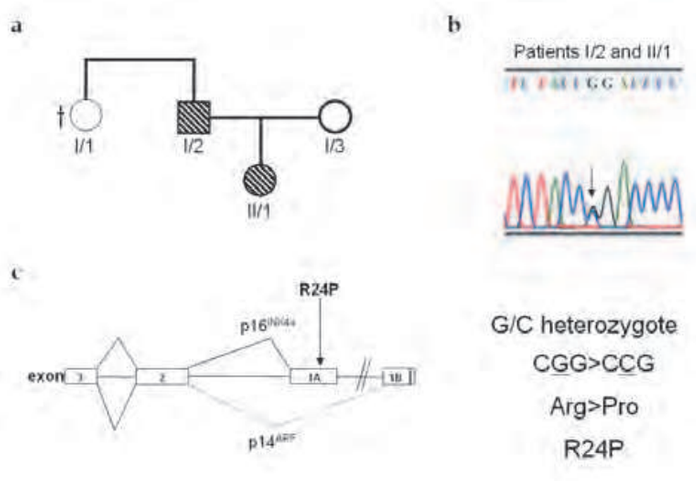

Fig. 4. Genetic analysis of the patient and her family. The 33-year-old female patient (II/1, melanoma, breast and pancreas carcinoma), her father (I/2; gastric and laryngeal carcinoma) and her mother (I/3; without any malignant diseases) were investigated. The father's sister (I/1) had died from breast cancer at a young age several decades ago, therefore her genetic investigation could not be performed (a). Sequence analysis revealed that probands I/2 and II/1 carried a missense mutation (G/C) in exon 1a of the CDKN2A gene (b), causing an arginine to proline amino acid change in codon 24 (R24P) affecting only the $p16^{INK4a}$ transcript variant (c).

Because of the occurrence of breast adenocarcinoma in our patient's medical history, it was also tested whether she carried mutations in the BRCA1 and BRCA2 genes. The 15 most commonly occurring (so-called "hot spot") BRCA mutations were studied (Table 1), but according to the sequencing data, none of them could be detected in the case of the female patient. After having received these data, we did not perform the BRCA1 and BRCA2 examinations on the genetic material of her father.

Based on these results, we hypothesize that the detected R24P mutation of the CDKN2A gene may be responsible for the melanoma and pancreas carcinoma of the 33-year-old female patient. At the same time, it may have contributed to the genetic predisposition for the breast cancer of our patient and her late aunt, as well as to the gastric and laryngeal carcinoma of her father. In the coming chapter we review current literature data about the possible breast cancer predisposing nature of CDKN2A mutations in general and the R24P mutation in particular.

2.3 The R24P mutation of CDKN2A has been worldwide implicated as a melanoma-predisposing genetic factor

The R24P germline mutation of the CDKN2A gene was first described by Australian authors. Holland et al. (Holland et al., 1995) reported on a survey performed on 17 melanoma-prone families in 1995 and they identified this mutation in one of the studied families. Since that time many independent studies proved the melanoma-predisposing nature of this mutation being one of the most widespread among the so-far identified disease-associated mutations of the CDKN2A gene. Soon after the first detection, the R24P mutation was also identified in US melanoma-prone families as early as in 1998 (Monzon et al., 1998) and its function was also assessed by yeast two-hybrid assay. According to the results, the R24P missense mutation almost completely abrogates the binding activity of the protein, thus explaining the disease-predisposing nature of the mutation. Following the "New World" publications of the R24P mutation, authors also reported it in European melanoma-prone families: it was reported in 1998 in the UK (MacKie et al., 1998) in the case of a relatively young (y31) male patient with multiple primary melanomas and in the case of two unrelated melanoma-prone kindreds in France (Soufir et al., 1998). This is why review papers from the mid-2000s refer to the R24P mutation as one of the most widespread CDKN2A mutations in the World, contributing to the genetic predisposition to familial, as well as multiple primary melanoma. To our best knowledge, ours is the first report on the identification of the R24P mutation in a Central-European family.

Taken together, the above summary well reflects that the R24P CDKN2A mutation is a relatively frequent one all over the World. Whether it is an ancient founder mutation that was spread to many geographical locale in the past, or independent mutation events happened, would be interesting to investigate (Table 2). There have been already very good examples provided where similar intriguing questions were addressed. Hashemi et al. (Hashemi et al., 2001) demonstrated that the 113insR CDKN2A mutation found only in Southern Scandinavia is a founder mutation that arose approximately 98 generations ago. Similarly, the G101W mutation that is frequent in Northern Italy, Southern Germany and France, is also a founder mutation that arose approximately 97 generations ago (Ciotti et al., 2000). Although the mutations appeared around the same time, the latter one is spread worldwide, while the Scandinavian 113insR could not be so far identified in any other geographical locale apart from Sweden. In view of these findings, it would also be very interesting to perform the haplotype mapping of R24P carrier patients to figure out whether it is also a founder mutation and if so, when it occurred in the past.

Gene and Mutation	Primers
BRCA1 3135delCATT	TCTGGGTCCTTAAAGAAACAAAGTC
	ACTTGGAATGTTCTCATTTCCC
BRCA1 3153delAG	CATCTCAGTTCAGAGGCAACG
	TGCATGACTACTTCCCATAGGC
BRCA1 3875delGTCT	TCACCCATACACATTTGGCTC
	AATCCATGCTTTGCTCTTCTTG
BRCA1 4184delTCAA	CGTTGCTACCGAGTGTCTGTC
	GACGTCCTAGCTGTGTGAAGG
BRCA1 185delAG	GGTTGGCAGCAATATGTGAAA
	TGCAGAACCAATCAAGACAGA
BRCA1 300T>G	GGCTCTTAAGGGCAGTTGTG
	AGAAAGGCAGTAAGTTTCTAATACCTG
BRCA1 1294del40	TGTAATGATAGGCGGACTCCC
	CTCAGGATGAAGGCCTGATG
BRCA1 2382GT	GACATGACAGCGATACTTTCCC
	TGTTGCACATTCCTCTTCTGC
BRCA1 5382insC	GTGTCTGCTCCACTTCCATTG
	CGAGACGGGAATCCAAATTAC
BRCA2 6079delAGTT, 6174delT, 6274delT	GTTGTTACGAGGCATTGGATG
	GGAAACTTGCTTTCCACTTGC
BRCA2 8034insAG	TATGGCAGATTTAGCAGGAGG
	TCGAGAGACAGTTAAGAGAAGAAAGA
BRCA2 8138delCCTTT	CTGGCCTCAAGCAATCCTC
	TTGACATGGAAGTCACAGACTACAC
BRCA2 9326insA	TCCACTACTAATGCCCACAAAG
	CACCTCAGAACAAGATGGCTG

Table 1. Hotspot mutations of the BRCA1 and BRCA2 genes and the primers used for the amplification of the surrounding gene regions.

Cancer-prone families identified to carry the R24P CDKN2A mutation			
Cancer types detected in the pedigrees	**Geographic locale**	**Authors**	**Date of publication**
Melanoma	Australia	Holland et al.	1995.
Melanoma	Canada	Monzon et al	1998.
Melanoma	France	Soufir et al.	1998.
Melanoma	U.K.	Mackie et al.	1998.
Sarcoma Melanoma* Cancer of the esophagus* Pancreas carcinoma* Carcinoma of the mouth and throat* Colon carcinoma* Lung carcinoma* Cancer of the gallbladder* Breast carcinoma*	North America	Lynch et al.	2002.
Melanoma Bladder cancer	Italy	Landi et al.	2004.

* The mutation was not identified in the late carcinoma patients but in a descendant with sarcoma.

Table 2. Publications on the R24P CDKN2A mutation and cancer types detected in the R24P families.

2.4 CDKN2A germline mutations in multiple primary malignancies

The idea that CDKN2A mutations may contribute to the predisposition of other primary malignancies beside melanoma came early in the middle of 90s, right after the identification of the gene's role in melanoma predisposition. Monzon et al. (Monzon et al., 1998) performed epidemiology and genetic studies on multiple primary melanoma cases and melanoma cases associated with multi-organ primary malignancies. They found that about 5 percent of patients have one or more additional primary lesions. This higher-than-expected prevalence of multiple primary melanomas may be due to excessive sun exposure, but according to the authors, genetic basis may also lay behind the phenomena. As supporting data, Monzon et al. claimed that patients with multiple primary melanomas very often have a family history of the disease. From epidemiology studies it was already known at that time that approximately 10 percent of melanoma cases have family background, which suggested genetic predisposition. Moreover, in 20 percent of the familial melanoma cases CDKN2A mutations could also be detected. The authors also claimed that in such families pancreas cancer also has a higher prevalence (Monzon et al., 1998).

The first in-depth analysis of this topic was reported in 1995 (Goldstein et al., 1995) by Goldstein and colleagues who compared the prevalence of other tumours in melanoma-prone families harboring or not harboring CDKN2A mutations. According to their analysis, CDKN2A mutation-harbouring melanoma-prone families have a 13-fold increased risk to develop pancreas cancer compared to those who do not carry such mutations. There was only one breast cancer patient mentioned in the paper who carried a mutant CDKN2A allele, while no breast cancer case could be detected in the group of melanoma-prone families with wild type CDKN2A alleles. The authors cited previous contrasting data demonstrating that the incidence of other types of cancers in melanoma-prone families in the US is not increased (Bohn et al., 2010). Moreover, another workgroup in the 80s suggested that patients with familial melanoma even had fewer other types of cancers than those suffering from sporadic melanoma (Kopf et al., 1986). These early data had been overwritten since and it is mainly due to the combined in-depth epidemiological and genetic studies performed within this special group of melanoma patients in the last 20 years.

As CDKN2A mutation studies became more and more intensive with the enrolment of centres from all over the world from Australia to the US through Europe, not only the genetic predisposition of familial melanoma but also its co-morbidities became recognized. This is a bright example of how genetic examinations can inspire epidemiological studies and shed light to connections of different diseases and their common predisposing factors. With reviewing several relevant papers we aim to demonstrate the above notion.

As early as 1999, Ghiorzo et al. (Ghiorzo et al., 1999) reported that the most prevalent malanoma-predisposing mutation of the Mediterranian, the G101W, was associated not only with a higher incidence of pancreatic malignancies, but also with breast cancer. In contrast, melanoma-prone families from the same geographical locale without CDKN2A mutations did not exhibit any non-melanoma neoplasias. The authors emphasized that the clinical-epidemiological study was conducted in a small geographical region where the sun and other types of environmental exposures of the individuals were approximately the same, therefore, differences of environmental factors could not account for the differential appearance of disease phenotypes. The authors therefore suggested that determining the underlying CDKN2A mutation in melanoma-prone families may have important implications not only for melanoma but also for further non-melanoma risk assessments.

In 2002, Lynch et al (Lynch et al., 2002) published the results of a survey where they aimed to elucidate the genetic background of the so-called FAMMM-pancreas carcinoma syndrome. They reported that their familial pancreas carcinoma database comprises of 159 families, of which 19 (12%) showed the FAMMM cutaneous phenotype. Lynch and co-workers studied the family tree, the history and the genetic background of eight families in detail. Most of the families had five-generation history of cancer where pancreas carcinoma predominated, but many other types of cancers were also prominent. A female patient of one of the families exhibited very similar multiple primary tumours as our 33-year-old patient: she had melanoma malignum, pancreas carcinoma and breast cancer with an onset at the age of 51, 56 and 61, respectively. Although the two patients exhibited a very similar pattern of tumours, there are two striking differences. The patient in the US study was already over the age 50 when her "march" of diseases started, while the Hungarian patient we are reporting now was only at the beginning of her 30s when the multiple primary tumours started. The other difference is that in the case of the Hungarian patient a melanoma-predisposing CDKN2A mutation could be detected, while in the case of the US female patient no such mutation was apparent. At the same time, Lynch et al. could also detect the previously described R24P mutation in another family of the study. In that extended family, a broad spectrum of cancers was apparent with the dominancy of pancreas carcinoma and malignant melanoma. In the case of a female family member, breast carcinoma was detected at her age of 60, but there was no report on any other malignancies. Whether she had any other predisposing genetic factors (eg BRCA1 or BRCA2 mutations) or her case was considered as a sporadic one is not discussed in the paper. Lynch et al. drew the conclusion that the cancer spectrum of the studied families in concert with CDKN2A mutations suggest a new putative hereditary carcinoma syndrome referred to as FAMMM-PC. The big variety of other types of cancers they demonstrated in the eight studied families raise the possibility that the predisposing CDKN2A mutations may contribute not only to FAMMM and PC but also to other types of malignancies, too. In this respect the case we present in this paper is also a supporting one to confirm the notion of Lynch et al.

Since Lynch and co-workers provided the first genetic study in FAMMM-PC syndrome (Lynch et al., 2002), the existence of such an entity became widely accepted and recent papers from various geographical locale were published in this topic. Bartsch and co-workers performed a survey in German pancreas cancer-prone families. Out of 110 such families, they identified 18 in which both melanoma and pancreas cancer occurred. The 18 families could be divided into two subgroups: five families with FAMMM-PC syndrome and 13 PC/melanoma families without the multiple mole phenotype (PCMS families). The authors found that the co-occurrance of pancreas carcinoma and melanoma was similar in the two subgroups; however, the prevalence of other tumour types, especially breast carcinoma was significantly higher in the latter group. Bartsch et al. checked CDKN2A germline mutations and mutations of genes contributing to breast cancer susceptibility. They identified CDKN2A mutations in 2 of the PCMS families but they could not identify any breast cancer susceptibility ones, only a co-segregating BRCA2 variant in a PCMS family without breast cancer. The conclusion they drew from the above was that families with an accumulation of pancreas cancer and melanoma show a large variety of phenotypic expression. Finally, the authors warn that more PC/melanoma families need to be analysed to clarify whether they represent a variation of the FAMMM-PC syndrome or there are two distinct hereditary cancer syndromes. The case we present in this paper may be considered as a reflection to their call since the family we studied does not show the multiple mole

phenotype. It may be classified as a PCMS family with an apparent CDKN2A mutation that is responsible for the malignant melanoma and pancreas carcinoma and possibly also contributing to breast carcinoma.

In an extended study performed in Southern Scandinavia, Borg et al. (Borg et al., 2000) found that patients carrying the 113insArg melanoma-predisposing founder mutation, pancreas carcinoma and as the second most frequent malignancy, breast carcinoma can also be frequently detected. The authors studied nine 113insArg mutation-carrying families and 42 CDKN2A mutation-free melanoma-prone families. The incidence of multiple primary malignancies was significantly higher in 113insArg families compared to those free of any genetic alteration in the CDKN2A gene. Borg et al. therefore claimed that the CDKN2A 113insArg mutation carriers have an increased risk not only to malignant melanoma but also to pancreas and breast cancer.

Prowse et al. presented a very elegant work in 2003 (Prowse et al., 2003) with an approach from the opposite direction. They studied BRCA1 and BRCA2 mutation-free breast cancer-prone families presenting multiple cases of early onset breast cancer and tried to find out what type of other gene mutations could predispose them to develop the disease. According to their estimation, only one third of breast cancer-prone families carry either BRCA1 or BRCA2 mutations, therefore other candidate genes contributing to disease predisposition must also be considered. The fact that eight families out of the 31 reported multiple cases of pancreas cancer and malignant melanoma prompted the authors to study the CDKN2A gene in detail. In one of the studied families, a novel CDKN2A mutation was identified: the IVS1-1G>C intronic mutation. The nucleotide substitution occurs at a highly conserved base in the 3′ splice junction of intron 1, thus both $p16^{INK4a}$ and $p14^{ARF}$ transcript variants are affected. The authors performed a functional analysis to prove that the mutation indeed causes the emergence of an aberrant splice variant. Owing to the fact that two proteins playing pivotal role in cell cycle regulation are affected by the same mutation, it is plausible to hypothesize that it may be of key importance in predisposition to various forms of malignancies.

Up to this point rare mutations of the CDKN2A gene were discussed in relation to predisposition to melanoma and other malignant diseases. However, a Polish workgroup also provided data on a relatively common variation of the same gene, the A148T polymorphism also contributed to disease pathogenesis. Debniak and co-workers (Debniak et al., 2005b) first showed that the A148T variant having a 3% allele frequency in the general Polish population was a melanoma-predisposing factor with an odds ratio of 2.5. Next they studied whether the same variant exhibits breast-cancer-predisposing nature too and found that the odds ratio associated with the CDKN2A allele for women diagnosed with breast cancer before the age of 50 was 1.5 and after the age of 50 it was 1.3. The effect was the strongest for women diagnosed at or before the age of 30 (Debniak et al., 2005a), suggesting a role of the A148T polymorphism in breast cancer predisposition. As a next step, the workgroup performed a population-based study where they compared the genotypes and the allele frequency of the A148T polymorphism in the group of 3,583 unselected cancer cases and 3,000 random controls. They found a positive association between the A148T variant and lung cancer and colorectal cancer with odds ratios of 2.0 and 1.5, respectively. The authors concluded that the A148T variant of the CDKN2A gene may contribute to multi-organ cancer risk (Debniak et al., 2006). How this variant reveals its disease-predisposing effect is still unclear. It has been demonstrated that the A148T allele did not have a major effect on the protein function (Ranade et al., 1995; Lilischkis et al., 1996);

however, according to Debniak and co-workers (Debniak et al., 2005a) we can not exclude the possibility that it subtly affects $p16^{INK4a}$ function or reduces its level of expression. Moreover, they could demonstrate that the A148T variant is in strong linkage disequilibrium with a promoter polymorphism of the CDKN2A gene, the P493 variant (Debniak et al., 2005b). Taken together, the Polish workgroup provided a very demonstrative set of data suggesting that beside the rare variants with high penetrance, a relatively common low-penetrance CDKN2A variant may also contribute to the pathogenesis of various cancer types. These findings may gain importance in the discovery of the pathogenesis of both familial and sporadic cancers.

The melanoma-predisposing nature of the A148T CDKN2A polymorphism have so far been most extensively studied in the Polish population, but sporadic data on the same variant exist in other populations. For example, Nagore and co-workers (Nagore et al., 2009) reported on the identification of two women in the Spanish population carrying the same A148T CDKN2A polymorphism and one of them having a hereditary breast/ovarian cancer family pedigree. At the same time, the authors claim that they could not find a significant difference in the allele frequency of the A148T variant in the general Spanish population and the studied breast cancer/melanoma patients' population. Nagore et al. could identify two more CDKN2A mutations in their study population: the V59G and the A85T, both of them frequently occurring in women suffering from both malignant melanoma and breast carcinoma. As a conclusion, the authors claim that because CDKN2A mutations are infrequent in female patients with melanoma and breast cancer, other deleterious variants such as mutations in BRCA1, BRCA2, TP53 must be studied in these types of patients' groups.

The above notion of Nagore et al. was confirmed by Monnerat and co-workers (Monnerat et al., 2007) who studied BRCA1, BRCA2, TP53 and CDKN2A genes in a group of female patients presenting both melanoma and breast cancer. The authors found that patients with a positive family history of both of these malignancies often carry variants of the aformentioned genes with a higher frequency than those without a family history. This study and all the above cited ones prompt us to draw two important conclusions: the co-occurrence of primary multi-organ malignancies are very often genetically determined but to reveal the exact pattern of genetic variants (the combination of high- and low-risk susceptibility factors), a well-defined set of genes must be studied in detail in large cohorts of patients. At the same time, we believe that single cases, for instance the one we present in this report, may add valuable data to the topic.

Until the mid-2000s, there was no opportunity to study the co-morbidities of familial melanoma in large cohorts of patients. The international GenoMEL Consortium, however, made it possible to perform large scale surveys in this topic and several hundreds of melanoma-prone families could be investigated both for their genetic predisposition and for their co-existing malignancies. Goldstein and the co-workers (Goldstein et al., 2007) of the GenoMEL Consortium published the results of their large scale survey in 2006. They studied 385 melanoma-prone families and out of them 39% carried one of the melanoma-predisposing CDKN2A mutations. The lowest ratio of such mutation carriers was identified in Australia, where the incidence of sporadic melanoma is higher than that of in Europe and in North America. This difference is also reflected in the relationship between pancreas cancer and CDKN2A mutations: while within the European and North American melanoma-prone families a clear connection could be identified between the mutation carrier status and pancreas carcinoma, no such relationship could be discovered in the

Australian patients. The authors hypothesize that the lack of pancreas cancer-CDKN2A mutation relationship in Australia reflects the divergent spectrum of CDKN2A mutations detected in Australian melanoma-prone families *versus* those from North America and Europe. In a follow-up paper (Goldstein et al., 2006), the authors extended their survey to neural system tumours and to uveal melanoma but found no association between CDKN2A mutations and these two malignancies either.

3. Conclusion

In this paper we presented the case of a 33-year-old female patient with the occurrence of three primary multi-organ malignancies, malignant melanoma, pancreas and breast carcinoma within a short period of time. The family history of the patient prompted us to perform a genetic study and we identified the melanoma-predisposing R24P CDKN2A germline mutation in her case as well as in her father, suffering from gastric and laryngeal carcinomas. Since the late aunt of the young female patient died of breast cancer at the age of her 20s several decades ago, we also surveyed the patient for the presence of BRCA1 and BRCA2 hotspot mutations but found no alterations in her case. Although we can not exclude the possibility that other predisposing gene variants may have contributed to the breast cancer of the patient, we suggest that the disclosed R24P CDKN2A mutation may have played a key role in the pathogenesis of her multi-organ primary malignancies.

Surveying the relevant literature clearly revealed that CDKN2A germline mutations are highly accepted as predisposing genetic factors for patients who suffer from co-existing pancreas carcinoma and malignant melanoma. However, no such consensus exists for the association of CDKN2A germline variants and the primary multiple occurrence of melanoma malignum and breast cancer. Studies performed in relatively small cohorts of patients resulted in contradictory data: some of them supporting while others rejecting the notion of the breast cancer-predisposing nature of CDKN2A germline mutations. To resolve this problem, extended studies on a wide range of low- and high-penetrance genetic predisposing factors must be examined on a multicentric base. We believe that single cases such as the one we presented in this paper may contribute to the understanding of the role of genetic susceptibility and environmental factors in the pathogenesis of multiple primary malignancies.

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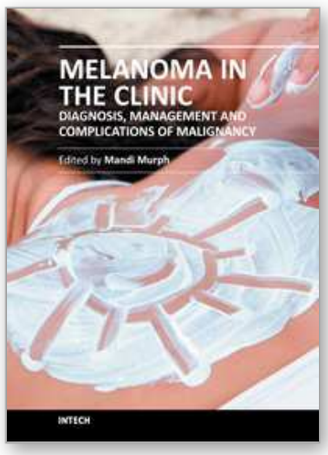

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This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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