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Combined Melanocytic and Sweat Gland Neoplasm: Cell Subsets Harbor an Identical HRAS Mutation in Phacomatosis Pigmentokeratotica

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Abstract

Phacomatosis pigmentokeratotica (PPK) is characterized by the co-existence of epidermal nevi and large segmental speckled lentiginous nevi of the papulosa type. PPK, previously explained as “twin spot” mosaicism due to the post-zygotic crossing-over of two homozygous recessive mutations, has recently been shown to derive from one postzygotic activating RAS mutation. Epidermal nevi, including those in PPK, are known to give rise to neoplasms such as trichoblastoma and basal cell carcinoma. Within speckled lentiginous nevi, Spitz nevi and melanoma have been well documented. We report a case of PPK with a combined melanocytic and adnexal neoplasm presenting where the nevi conjoined. Using next generation sequencing techniques, we were able to identify the same HRAS G13R mutation within both components of the tumor, and to show the absence of additional mutated modifier genes in a panel of 300 cancer-related genes. Given the genetic findings in this rare tumor-type, we suggest that this case may be used as a model for understanding the development of biphenotypic neoplasia or intratumoral heterogeneity in some cases.

Keywords

linear verrucous epidermal nevus; pigmented nevus; mutation

Introduction

Phacomatosis pigmentokeratotica (PPK) is a rare syndrome of genetic mosaicism characterized by the coexistence of epidermal nevi and large segmental speckled lentiginous nevi of the papulosa type. Epidermal nevi, including those in PPK, are known to contain neoplasms such as trichoblastoma and basal cell carcinoma.(1) Within speckled lentiginous nevi, Spitz nevi(1, 2) and melanoma(1, 2) have been well documented. In addition,

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telangiectatic macules, collagenomas and generalized ichthyosiform hyperkeratosis have also been associated with PPK.(2, 3) Combined tumors, neoplasms that are composed of more than one tumor type, excepting morphologically heterogeneous adnexal neoplasms, have rarely been reported in either of these nevi.

The formation of combined tumors is usually explained by divergent differentiation of a multipotent precursor cell, simultaneous tumorigenesis of two adjacent different cell types under the influence of the same oncogenic stimulus, dedifferentiation or re-directional differentiation of an already differentiated tumor, or random physical collision. Commonly reported variants of combined tumors in the skin include squamous and neuroendocrine carcinomas,(4) squamous and basal cell carcinomas,(5) and less commonly, melanocytic and basal cell(6) or squamous cell carcinomas.(7)

We recently observed the occurrence of an unusual combined melanocytic and adnexal neoplasm, which arose within the overlap region of an epidermal nevus and a speckled lentiginous nevus. Using targeted next generation sequencing on tissue derived from microdissected tumor components, we identified, from a panel of 300 cancer related genes, only a single, identical HRAS mutation in each component of the combined tumor. Based on this finding, we propose that the underlying mosaic RAS mutation within two different adjacent cell types, derived from a distant shared progenitor cell, was the initiating event that rendered them susceptible to neoplastic transformation by a common, as of yet undetermined additional influence, thus resulting in the development of a biphenotypic or “combined” tumor. We suggest that such a mosaic RASopathy may be used as a model to explain the development of combined tumors or intratumoral heterogeneity in other settings.

Materials and Methods

Specimen acquisition

With IRB approval, formalin fixed paraffin embedded tissue blocks from the patient’s combined tumor were obtained from the pathology archive. For control genomic DNA, with the patients consent, peripheral blood samples were obtained. Hematoxylin and Eosin stained tissue sections were evaluated for morphologic features. Immunohistochemical stains (table 1) were assessed for cellular differentiation antigens and to define boundaries of tumor components.

Laser capture microdissection

Laser capture microdissection (LCM) was performed on individual tumor components of tumor-bearing tissue using Veritas Microdissection System (Arcturus, Life Technologies). For LCM, FFPE tissue sections 4–5 µm thick were placed on PEN membrane slides and stained with hematoxylin alone. Multiple serial sections (10–20) of tissue were used to maximize yields. Between, 5000 – 10,000 cells were harvested from two different areas of the tumor to obtain pure cell populations of melanocytes or epithelial cells, carefully avoiding inflammatory cells. Cells collected in LCM caps were pooled together in eppendorf tubes for DNA extraction.

DNA extraction

From the microdissected tissue, DNA was extracted and purified according to the protocol for DNA isolation from FFPE tissue, from Agilent Oligonucleotide Array-Based CGH for Genomic DNA Analysis (Agilent technologies, Santa Clara, CA). Genomic DNA was extracted from peripheral blood samples using the Blood and body fluid spin protocol with QIAamp DNA blood mini kit according to the manufacturer's protocol (Quiagen, Hilden, Germany).

Targeted next generation sequencing

We profiled genomic alterations in 300 key cancer-associated genes using our IMPACT assay (Integrated Mutation Profiling of Actionable Cancer Targets), using custom oligonucleotides for hybridization capture of all protein-coding exons and select introns of these genes. Bar-coded sequence libraries were prepared (New England Biolabs, Kapa Biosystems) and exon capture was performed (Nimblegen SeqCap) as previously described (8). 31 to 80 ng of genomic DNA was input for library construction. Libraries were pooled at equimolar concentrations (100 ng per library) and input to a single exon capture reaction. To prevent off-target hybridization, we spiked in a pool of blocker oligonucleotides complementary to the full sequences of all bar-coded adaptors to a final total concentration of 10 micromolar. DNA was subsequently sequenced on an Illumina HiSeq 2500 to generate paired-end 75-bp reads. Sequence data were demultiplexed using CASAVA, and reads were aligned to the reference human genome (hg19) using the Burrows-Wheeler Alignment tool (9). Local realignment and quality score recalibration were performed using the Genome Analysis Toolkit (GATK) according to GATK best practices (10). We achieved a mean unique sequence coverage of 374X per sample. Single-nucleotide variants were called using muTect (11) and retained if the variant allele frequency in the tumor was >5 times that in the matched normal. Indels were called using the SomaticIndelDetector tool in GATK. All candidate mutations and indels were reviewed manually using the Integrative Genomics Viewer (12).

Results

Patient Case Report

An 18-year-old female presented with a history of a linear epidermal nevus, a nevus sebaceus, and speckled lentiginous nevi. She was born to nonconsanguineous parents with an unremarkable family history. She had multiple surgical excisions of the nevus sebaceus on her face prior to presentation. She also had ultrapulsed carbon dioxide laser treatments of the linear epidermal nevus of the right ear and neck. On presentation in 2005, at the age of 13, a speckled lentiginous nevus involved her left and right face, right chest, arm, and back, buttocks, and right anterior and posterior thighs (Fig. 1A). She had lower extremity hemiatrophy, but no other neurologic, skeletal, or ocular abnormalities. Magnetic resonance imaging of the brain done at a younger age was normal. She was monitored clinically for changing lesions for the next 4 years, with excisions for Spitz, junctional, and dysplastic compound melanocytic nevi within the region of the speckled lentiginous nevus. In 2009, at 18 years of age, she developed, within one epidermal nevus on the posterior scalp/upper neck, a 1.5cm erythematous, keratotic nodule with serous and hemorrhagic crusts and

occasional bleeding (Fig. 1B). There was concern for squamous cell carcinoma and a shave biopsy was obtained.

Histopathology and Immunohistochemistry

By histopathology, the neoplasm appeared somewhat circumscribed, and was comprised of an intermingled admixture of an adnexal neoplasm and melanocytic proliferation (Figs. 2A, B, C). On the surface, the adnexal neoplasm showed an invagination of squamous lined epithelium, which transitioned to a 2-cell layer apocrine-type epithelium overlying islands of intradermal plasma cells diagnostic of syringocystadenoma papilliferum (Figs. 3A). Within the underlying dermis, encased by a sclerotic stroma, was a glandular proliferation of pale cells with 2 cell layers (Fig. 3B), including an inner cuboidal cytokeratin positive epithelial layer (Figs. 2B, 3C, 3D), and a flattened outer myoepithelial layer. Melanocytes were arranged as irregular nests along the dermoepidermal junction, and within the superficial dermis, with deep extension along the neoplastic adnexal epithelium. Melanocytes were large, with vesicular nuclei, prominent nucleoli, and abundant cytoplasm.

Immunohistochemical stains for S-100 (Fig. 2C), Melan-A (Fig. 3E), and HMB-45 highlighted the melanocytic component, demonstrating a benign symmetric pattern of growth. S100 also highlighted the myoepithelial component of the adnexal proliferation (Fig. 3F). Epithelial markers AE1:AE3, Cytokeratin 7 (Fig. 3C, D) and Carcinoembryonic antigen were negative in this proliferation. Mib-1 staining was very low. Altogether the findings were best interpreted as a combined syringocystadenoma papilliferum and tubular adenoma, and an atypical melanocytic nevus (Fig. 4A).

Subsequently the tumor was excised. Focal residual combined tumor was identified at the base of the scar. Of note, on examination of both specimens, it appeared that the two lesions shared the same physical confines (Fig. 4B). No more atypical changes were identified. The post-op course was unremarkable, and the lesion has not recurred.

In 2011, the patient developed a new lesion on the right ear that was biopsied and interpreted as syringocystadenoma papilliferum and a focal basaloid proliferation within the background of nevus sebaceus. This lesion was excised without recurrence. A 2012 biopsy revealed a combined verrucous keratosis and intradermal melanocytic nevus, and in 2013, a biopsy of an eyebrow lesion revealed a tumor most consistent with trichilemmoma.

Mutational status

An identical HRAS c.37G>C (p.Gly13Arg) mutation was identified in tumor tissue from both microdissected components of the keratinocytic adnexal and melanocytic tumor by use of the IMPACT assay (Figure 3). DNA from the blood showed a wild-type sequence for HRAS. No additional mutations were identified within either component of the tumor or peripheral blood.

Discussion

Phakomatosis pigmentokeratotica (PPK), a term coined by Happle in 1996,(13) describes a distinct type of epidermal nevus syndrome which arises due to genetic mosaicism. The two components of PPK include an epidermal nevus (organoid-type with sebaceous

differentiation) and a speckled lentiginous nevus of the papular type. The epidermal nevus appears along the lines of Blaschko, a visible manifestation of embryonic routes of cellular migration. The speckled lentiginous nevus appears in a checkerboard pattern. The genetic mosaicism gives rise not only to two characteristic cutaneous morphologies, but also to corresponding syndromes with extracutaneous manifestations. The epidermal nevus may present along with mental retardation, seizures, ophthalmologic abnormalities, skeletal defects, and vascular anomalies, termed the Schimmelpenning syndrome.(14, 15) The speckled lentiginous nevus syndrome presents with neurologic abnormalities such as sensory and motor neuropathies and palsies, muscular atrophy or hypertrophy, and hyperhidrosis.(16, 17) PPK has also presented along with a rhabdomyosarcoma(17) and hypophosphatemic rickets.(2) Our patient showed only musculoskeletal hemiatrophy in addition to her skin findings.

Generally, the epidermal and melanocytic proliferations in PPK remain as benign hamartomas. However, epidermal nevi of PPK have given rise to basal cell carcinoma(1) and speckled lentiginous nevi of PPK have given rise to malignant melanoma.(1, 2) Outside the context of PPK, a variety of cutaneous neoplasms, including basal cell carcinoma, squamous cell carcinoma, porocarcinoma, and syringocystadenoma papilliferum(18–20) have been reported to arise within a nevus sebaceus. Syringocystadenoma papilliferum and tubular adenoma are two rare adnexal neoplasms that have been reported to arise together in a background of nevus sebaceus, though not in the context of PPK.(21–26) There has been only one previously reported case of melanoma arising from a nevus sebaceus.(27) However, malignant melanomas and Spitz nevi have been noted to develop within speckled lentiginous nevi.(1, 2) These phenomena are generally explained by the hypothesis that the large epidermal or melanocytic nevic patches represent “field defects” e.g. the speckled lentiginous nevus as a field defect with the potential for the development of diverse neural crest-derived cellular proliferations.(17) The underlying somatic mosaic mutation in these areas is thought to create an increased susceptibility to further oncogenic “hits”.

It was previously hypothesized that PPK occurred due to a postzygotic phenomenon, known as twin spotting, in which two homologous chromosomes undergo an early mitotic recombination of a double heterozygote to give rise to two homozygous recessive alleles. The two subpopulations of cells carrying their two different respective mutations would then migrate adjacent to each other during embryonic development and give rise to adjacent lesions in specific patterns,(28) constituting a “double mosaic” phenotype. Mutations in PPK were hypothesized to affect loss of function (tumor suppressor) genes(13, 29, 30) which would lead to an increased risk of cancer in the lesional tissue.(31), However, recently, postzygotic somatic mosaicism of an activating RAS mutation was identified in two patients with Schimmelpenning syndrome and a nevus sebaceus(32). In one patient, the HRAS mutation was found in the nevus sebaceus as well as in a syringocystadenoma papilliferum which had developed within nevus sebaceus.(32) The mutations were not present in wild-type cells of either patient. Subsequent to this report, identical HRAS mutations were identified in a series of patients with PPK, within separate melanocytic and keratinocytic lesions (33). These studies have reclassified PPK into the category of a non-allelic mosaicism; in effect, a mosaic RASopathy in which the risk of tumorogenesis is increased. Unlike other mosaic RASopathies resulting in epidermal nevus syndromes (34) (35), in

PPK, the involved gene mutation most likely occurred prior to neural crest differentiation within a multipotent progenitor cell capable of giving rise to different cell lineages (melanocytes and keratinocytes) in order to result in the phenotype of altered melanocytic and keratinocytic tissues. In our patient, given the further finding of a skeletal anomaly, we would expect that the mutation occurred within a progenitor cell with both ectodermal and mesodermal differentiation potential.

The mechanism of development of combined tumors (herein referring to tumors which show more than one histopathologic and/or immunophenotypic line of differentiation) has been debated, and the theoretical mechanisms have been reviewed.(7, 36, 37). Suggested mechanisms include divergent differentiation of a multipotent precursor cell, simultaneous tumorigenesis of two adjacent cell lineages driven by a shared oncogenic stimulus, dedifferentiation or re-directional differentiation of a previously differentiated tumor, or random physical collision.

Huang et al, using clonality studies, have shown that the different histopathologic components of some combined tumors had identical genetic alterations, suggesting that the tumors were derived from a common precursor cell.(36) However, the divergent tumor components in all of those cases were epithelial types, making it difficult to generalize these findings to tumors with more diverse biphenotypism, such as our case and other examples of divergent combined neoplasms such as squamomelanocytic tumors,(37) basal cell carcinoma and melanoma collisions,(38) or squamous cell carcinoma with chronic lymphocytic leukemia.(39) In the latter types of cases, some authors have offered possible explanations including a shared paracrine influence by two separate precursors(7) or “colonization” of one tumor by the other without a shared precursor.(37) Overall, these kinds of combined tumors are rare.

The findings of Groesser et al give evidence for the concept that a single activating mutation in a multipotent cell during embryogenesis can be responsible for synchronous field defects in diverse tissue types, predisposing to the development of tumors within these different tissues(32, 33). In this context, our case illustrates one mechanism of forming a combined neoplasm: bidirectional differentiation of a mutated multipotent progenitor cell allowed for the physical proximity of two different cell types with a predisposition to tumor formation. These neighboring RAS-mutant cells thereafter underwent tumorigenesis in the presence of a shared, as of yet, unknown, additional influence. The findings of an identical HRAS G13R mutation within each tumor component support the conclusion of a shared, albeit distant precursor. The absence of the same mutation within peripheral blood confirms the mosaic phenotype. We were unable to find additional candidate modifier gene mutations in a panel of 300 cancer-associated genes. However, if we look to the recent findings of HRAS mutated squamous proliferations in the context of pharmacologic RAF inhibitions(40), we also consider the possibility of external physical or chemical mediation in the role of the “second hit” in cutaneous RASopathies, such as our case. Finally, while we do favor that this tumor arose synchronously due to a shared second mediator, we allow for the possibility of random physical collision of two tumors having evolved due to separate secondary influences in the background of their respective HRAS mutant nevic patches.

Conclusions

In conclusion, this case describes the unusual finding of a combined neoplasm deriving from a background of phacomatosis pigmentokeratolica, a syndrome caused by a postzygotic, pre-neural crest differentiated, RAS-mutant mosaicism, which sheds light on the mechanism of pathogenesis of some combined tumors. We suggest the possibility, that large nevus “twin spot” mosaicism could create the potential for histopathologically biphenotypic neoplasms. If this is the case, it is also possible that small non-clinically identifiable adjacent mosaic foci in diverse tissue types could result in a more subtle version of intratumoral heterogeneity or irregular foci of susceptibility to biphenotypic neoplasia. Further work is needed to examine the complex genetic features and pathogenesis of such tumors.

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Figure 1.

A. Speckled lentiginous nevus involving the upper back and shoulder in a “checkerboard pattern”, consisting of a large café au lait macule speckled with multiple dark brown irregular nevi. B. The keratotic tumor nodule, with variegated color, arising at the intersection of epidermal nevus/nevus sebaceus and speckled lentiginous nevus.

Figure 2.

A. Hematoxylin and Eosin. Scanning magnification shows the complex but circumscribed, admixed adnexal and melanocytic proliferation. B. A cytokeratin 7 immunohistochemical stain highlights adnexal epithelial cells of syringocystadenoma papilliferum and tubular adenoma, sparing adjacent epidermis and intermingled melanocytes C. S-100 immunohistochemical stain highlights melanocytes and myoepithelial cells of the tubular adenoma, showing the well-demarcated peripheral tumor boundary.

Figure 3.

A. Low power view of the combined tumor; the surface of the syringocystadenoma papilliferum is seen here as a squamous epithelium-lined invagination, with a 2-cell layer apocrine-type epithelium over clusters of plasma cells. On the lower left corner the well-defined tubular adenoma is represented. Melanocytes are seen best in the lower right corner. B. High power; a region within the center of the tumor where the ductal structures of the adenoma are colonized by and intimately admixed with the melanocytic component. C,D. Pancytokeratin AE1:AE3 highlights the adnexal neoplasm. E. Melan-A immunohistochemical stain labels the melanocytic component. F. S100 immunohistochemical stain labels the myoepithelial component of the adnexal proliferation, as well as nearby melanocyte nests.

Figure 4.

A. Hematoxylin and Eosin. A high power focus shows all three tumor components: plasma cell islands of syringocystadenoma papilliferum, well defined two-layered ductular structures of tubular adenoma, and melanocyte nests, “colonizing” the adenoma. B. The peripheral border of the tumor is delimited by both melanocytic and adnexal components.

Table 1

Antibody Data

Marker	Clone	Dilution	Manufacturer
S100	Rabbit Poly	1:8000	Dako Corporation; Carpinteria, CA
Mart1/Melan-A	A103	RTU	Ventana Medical Systems Inc, Tucson, AZ
CK7	OV-TL 12/30	1:200	Dako Corporation; Carpinteria, CA
Pan-Keratin	AE1:AE3 and PCK26	RTU	Ventana Medical Systems Inc, Tucson, AZ
Ki-67	MIB1	1:800	Dako Corporation; Carpinteria, CA
CEA (P)	Rabbit Poly	1:1000	Dako Corporation; Carpinteria, CA

RTU: Ready to use, CK: cytokeratin, CEA: carcinoembryonic antigen