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Sporadic melanotic schwannoma overlapping with features of melanocytoma bearing a GNA11 mutation in an adolescent girl

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Abstract

Melanotic schwannoma (MS) is a rare soft tissue neoplasm that shares histological features with both melanocytic tumors and schwannomas. A type of MS, called psammomatous melanotic schwannoma, is associated with Carney complex (CNC). CNC is caused by mutations in the *PRKAR1A* gene. Other pigmented neoplasms, like uveal melanomas (UM) and melanocytomas (MC) are associated with genetic defects in other genes, including *GNA11*. We report a case of an adolescent girl with a large sporadic mesenteric MS with complex histologic findings reminiscent of both PMS and MC. This lesion carried a mutation of the *GNA11* gene, which is considered highly specific for UM or MC. We conclude that sporadic MS may occur rarely in adolescents without CNC; MS may also be associated with somatic *GNA11* mutations.

Keywords

Psammomatous melanotic schwannoma; Carney complex; multiple neoplasia syndrome; protein kinase A; tumor genetics

Introduction

Schwann cells are neural crest cells originating from the ventral side of the neural tube. During embryogenesis, the bi-potent Schwann cell precursor can either stay in contact with the nerves and differentiate into Schwann cell, or detach and differentiate into melanocyte.[1]

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Conflict of Interest statement

The authors of the manuscript have no conflict of interest to declare.

The main function of the Schwann cells is the formation of the myelin nerve sheath, which facilitates the signal transduction.[2] Differentiated neoplastic Schwann cells form benign, slow-growing tumors, the schwannomas.[3]

The melanocytes are located on the epidermis, the hair follicles, the eyes, the brain and other body parts.[4,5] They enclose melanosomes, which are melanin containing organelles that contribute to their pigmented appearance. Melanocytes can be identified in various melanocytic tumors. Among these, melanoma is probably the most aggressive one and usually derives from the skin melanocytes.[6] Melanocytomas (MC) are rarer tumors, with slow growth, mainly located on the skin or the mucosal surfaces and have a much more favorable prognosis than melanomas.[7]

Melanotic schwannoma (MS) is a distinct, soft tissue neoplasm that shares histological features with melanocytic tumors and schwannomas; it is a grossly pigmented variant of schwannoma.[8] It is a very infrequent tumor, with a malignant potential. There are two types of MS; non-psammomatous and psammomatous melanotic schwannoma (PMS). PMS occurs rarely sporadically but mostly in association with Carney complex (CNC), an autosomal dominant syndrome characterized by abnormal skin pigmentation (lentigines and other lesions), myxomas, endocrine hyperactivity and multiple other neoplasias. [9]

To our knowledge, a mesenteric MS of the abdomen has not been reported in the pediatric population. We report a case of an adolescent presenting with a large sporadic abdominal mesenteric MS with overlapping features with melanocytoma, bearing a mutation of the *GNA11* gene, which is considered highly specific for uveal melanomas (UM) or MC. [10,11,12]

Materials & Methods

Clinical investigations

The patient was recruited under clinical protocol 95CH0059 (which studies patients with CNC and related disorders) to the National Institutes of Health (NIH) Clinical Center. Written informed consent was obtained from the parents, and the study was approved by the NICHD institutional review board.

Genetic & immunohistochemistry studies

DNA was extracted from peripheral blood leucocytes and tumor tissue according to commercially available protocols (QIAGEN, Valencia, CA, USA). DNA sequencing for candidate genes was performed using previously published methods for the respective genes.

Immunohistochemistry was performed on paraffin-embedded slides. Tumor material was sequenced of de-parafinized samples. Diagnostic testing to determine the type of the tumor was done with markers as presented below (see clinical case report).

Results

Clinical case report

A 16-year old female presented to a local hospital with acute abdominal discomfort and distention. Her initial laboratory evaluation revealed anemia with hemoglobin of 9.3 g/dL, that had decreased by 3g/dL within the past six months. Abdominal ultrasound showed a large mass and computed tomography (CT) of the abdomen and pelvis revealed an abdominal mass of 19×16×11 cm in the lower part of the peritoneal cavity extending to the pelvis with a dilated entering vessel. The density of the mass was heterogeneous, with cystic and solid components (Figure 1). Peritoneal fluid was also evident in the upper and lower abdomen. The patient within hours developed dizziness, vomiting, worsening of her abdominal pain with further decrease of the hemoglobin to 6g/dL and underwent urgent surgery. The surgically resected tumor was a sizeable cystic mass of the mesosigmoid containing a solid portion. The sizeable bleeding vessel at the bottom of the mass, possibly representing the supplying vessel, was ligated. Recovery was uncomplicated and at 10 months postoperatively the patient was referred to the National Institutes of Health for further clinical evaluation and examination of the tumor specimens.

The adolescent's physical examination was normal with no mucocutaneous lesions and no signs of organomegaly or endocrine hyperactivity. She had no family history of neural crest tumors, neurofibromatosis or CNC. Histopathology reported that the resected tumor was composed of relatively uniform spindled cells with variable melanin pigmentation (Figure 2). In addition, heavily melanin-pigmented cells, probably melanophages, were also seen. Both atypia and mitotic activity were low. Immunophenotyping for the melanocytic markers S100 protein, Sox10, HMB45, MelanA, and CD117 was positive, and negative for CD34, CD56, CD99, calretinin, desmin, DOG1/Ano1, EMA, inhibin, keratins (7, 8/18, 20), SMA, and synaptophysin. Ki67-index was approximately 5-7%.

Two independent experienced pathologists reported that the tumor's features were consistent with MS; however, one of the pathologists also identified characteristics of MC. Both pathologists agreed that the low index of growth and proliferation within the lesion did not identify it as having a high potential for metastasis. To this day, the patient remains well without any evidence of recurrence or distant lesions.

There were no obvious skin abnormalities, confirmed by detailed dermatological examination. The pituitary hormone profile was normal, with prolactin level of 19.7ng/ml (normal range 2-25ng/ml), IGF-1 level of 585ng/mL (normal range 143-859ng/mL) and appropriately suppressed morning serum cortisol concentration of <1mcg/dL after administration of low dose dexamethasone. MRI of the pituitary was normal. The echocardiogram was negative for myxomas and the ultrasound of the thyroid did not reveal any nodules. In order to exclude the presence of UM, a thorough ophthalmology evaluation was performed and was negative. Cerebrospinal fluid analysis showed no malignant cells on cytopathology and negative tumor markers (alpha-fetoprotein, human chorionic gonadotropin beta-subunit, and carcinoembryonic antigen). Whole body imaging, including by magnetic resonance (MRI) of the chest/abdomen/pelvis and positron-emission/CT (PET/CT) of the body were negative, with no evidence of recurrence or metastasis.

Molecular genetic studies

Molecular analysis of the tumor was positive for the mutation c.626A>T, p.Q209L on exon 5 of the *GNA11* gene, while the same mutation was not identified in the germline. Gene analysis of the tumor for the common mutations of the *BRAF* and *GNAQ* genes was negative, while both peripheral and tumor DNA were also negative for *PRKAR1A* gene mutations. The germline DNA was further tested for Copy Number Variants (CNVs) with array Comparative Genomic Hybridization (CGH), while whole exome sequencing was also performed with no identification of any further genetic abnormalities, including no mutations of the *NF2* gene, responsible for neurofibromatosis type 2 (NF2), or any other tumor genes.

Discussion

MS are extremely rare in childhood and adolescence. They usually occur in adulthood and affect males and females equally.[10] Sporadic tumors show a peak incidence in the fourth decade of life whereas tumors associated with CNC tend to occur at a younger age (peak incidence in the third decade of life).[13] MS may arise from various body parts, including the spinal nerve roots, the paraspinal symphathetic chain, cranial nerves, soft tissues, skin, heart, trachea, oral cavity, parotid gland, intraperitoneal and retroperitoneal organs of the gastrointestinal tract i.e. the esophagus, stomach, pancreas.[3, 14] A review of the literature to date, revealed only a few cases of MS that have been described in children and adolescents, aged 9-17 years, located in the spinal area, the heart and the soft tissues. Our patient presented with a large mesenteric sporadic MS that to our knowledge has not been previously described in the pediatric population.

The genetic characteristics of sporadic MS are largely unknown. Studies have shown genomic losses of chromosomes 1, 2, 17, 21 and 22.[11, 12] On the other hand, PMS in the context of CNC are due to germline mutations in the *PRKAR1A* gene.[15] Our patient did not have CNC, her tumor was not PMS, and did not carry *PRKAR1A* mutations. Instead, our patient's tumor harbored a *GNA11* gene mutation.

GNA11 gene and its homologue *GNAQ*, code for a Gq class alpha subunit of the heterotrimeric guanine nucleotide-binding protein (G-protein) receptor. In response to a ligand, the alpha subunit binds to GTP resulting in its dissociation from the βγ subunit and the activation of phospholipase C and the production of inositol triphosphate and diacylglycerol, leading to activation of the protein kinase C and the downstream MAPK pathway.[16] Mutations of either gene result in persistent linking of the alpha subunit to GTP, which causes the constitutive activation of the pathway.[16] *GNA11* mutations have been reported as a potential molecular marker to differentiate melanocytic tumors. In UMs and MCs, the gene mutations are common with a reported frequency of 32-57%, whereas in MS, *GNA11* gene defects have not been described.[17-19]

The finding of a *GNA11* gene mutation in the described tumor, which was characterized as MS with some characteristics of MC, suggests that this gene defect may not be as exclusive as previously thought. It also suggests that MS may originate from a cell precursor of both the Shwann cell and the melanocytes.[1, 20] In clinical practice that means that the

identification of a gene defect cannot be used as the sole factor to classify the different melanotic tumors. Overlapping histologic features of these lesions may add further to the diagnostic complexity. Instead, a combination of clinical, molecular and histologic findings should be used to ultimately determine the final diagnosis. Given the different nature of each disease, treatment options and recurrence rates, the characterization of these tumors is of high importance. Whether this case represents a variant of MS with different prognosis for recurrence or metastasis remains to be seen, although to this day the patient remains free of disease (approximately 3 years after the original diagnosis).

We conclude that sporadic abdominal MS may occur in adolescents rarely. MS may also be associated with somatic *GNA11* mutations, especially when histologic features of MC are also present, a finding that has implications for both prognosis and possibly the cellular origin of these tumors.

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Abbreviations

MS	Melanotic schwannoma
CNC	Carney complex
UM	Uveal melanomas
MC	Melanocytomas
PMS	Psammomatous melanotic schwannoma
NIH	National Institutes of Health
MRI	Magnetic resonance
PET/CT	Positron-emission/computed tomography
CNV	Copy Number Variant
CGH	Comparative Genomic Hybridization

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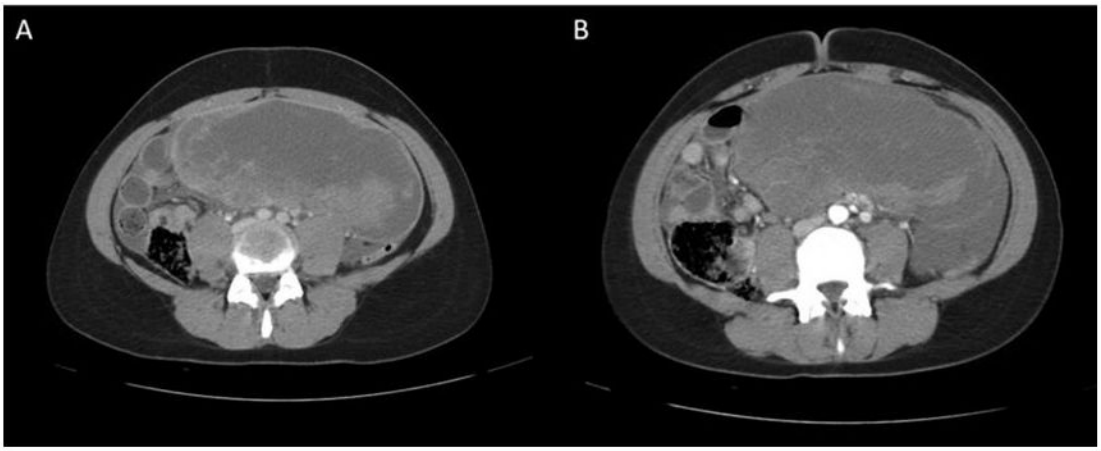

Figure 1:
CT images of the large intraabdominal mass with cystic and solid components (1A,B), showing no enhancement post contrast administration (1B).

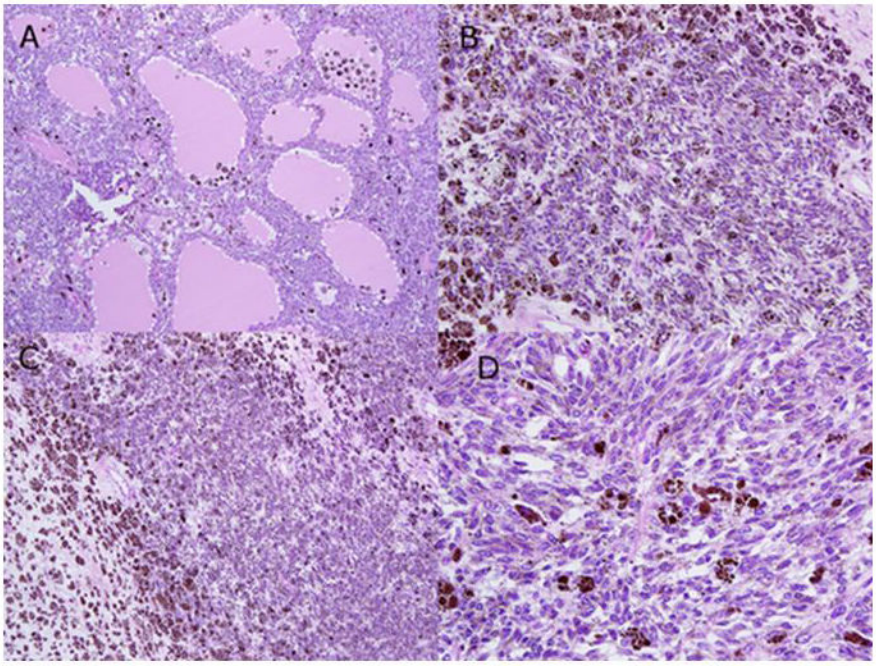

Figure 2:
Histopathology images of the resected tumor showing uniform spindled cells with variable melanin pigmentation.