Pitfalls and uncertain prognosis in pathological diagnosis of psammomatous melanotic schwannoma

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ABSTRACT

A 20-year-old woman presenting with a pelvic mass identified as a psammomatous melanotic schwannoma (PMS) with atypical histological features was later found to have family history of cardiac myxomas consistent with Carney's complex. The BRAF V600E mutation was absent in the tumor.

1. Case report

A 20-year-old woman patient presented an 8-year history of back pain radiating down the right leg into the foot leading to numbness in the S1 distribution. History obtained after surgery revealed that her father and others in the paternal family had cardiac myxomas.

MRI of the lumbosacral spine revealed a well-defined mass centered at the right S1 neural foramen demonstrating heterogeneous high T1-weighted (Fig. 1A, B) and low T2-weighted (Fig. 1C, D) signal, consistent with the presence of hemorrhage or melanin. The mass was predominantly extradural and caused marked narrowing of the thecal sac with likely compression of the right sacral nerve roots. There was remodeling of the neural foramen but no definite bone marrow infiltration. Tumors arising from bone or nerve sheath as well as metastases were considered diagnostic possibilities. The patient underwent a hemilaminectomy at L5-S1. Clearly hemorrhagic tumor material was visible within the capsule. Gross total resection was not achieved.

Hematoxylin and eosin stained sections, formalin-fixed, paraffin-embedded tissue showed a non-encapsulated solid tumor made of cells lying in a collagenous matrix. The cells had polygonal or slightly fusiform acidophilic cytoplasm, often containing abundant melanin granules. The nuclei were large, irregularly rounded, containing a large spherical eosinophilic (inclusion-like) nucleolus (Fig. 2A), and frequently empty vacuoles. Multinucleated cells were common. Pleomorphism was marked, with formation of bizarre nuclei, but mitotic figures, including atypical ones, were only occasionally found (Fig. 2B). The matrix showed punctate calcification condensed at multiple points into calcific masses of irregular shape with frayed or mulberry-like outline (Fig. 2C). There were areas of necrosis (Fig. 2D). Melanin and a palisading pattern arrangement of nuclei were present (Fig. 2E). Areas with intracytoplasmic vacuolization resembling adipose tissue were identified within the tumor (Fig. 2F). Tumor cells expressed nuclear and cytoplasmic S100, cytoplasmic Mart-1 and HMB-45 (Fig. 2G), and nuclear Sox10. There was no expression of GFAP or synaptophysin. P53 was expressed in occasional nuclei, the wild type pattern. The Ki-67 proliferation index was 10% (Fig. 2H). There was no labelling with an antibody (clone VE1) specific for the BRAF V600E mutation. PCR molecular studies revealed absence of mutations in exons 11, 13, 17, and 18 of the KIT gene and confirmed the absence of BRAF V600E mutation. NRAS analysis was attempted but amplification failed. Immunohistochemistry for CD117 (c-kit), found in literature to be positive in MSs, was negative [1,2].

The patient completed her course of postoperative radiotherapy of 60 Gy in 30 fractions in the weeks following the operation. Further MRIs 8 months after the operation indicated that the mass along the right S1 nerve root appeared stable, with no evidence of thoracic metastases. The patient was seen 1 year after the operation to discuss options for fertility preservation after radiation treatment.

2. Discussion

Melanotic schwannoma (MS) is a melanin-producing nerve sheath tumor [3,4]. 40–50% of MSs contain psammoma bodies and are thus designated psammomatous melanotic schwannomas (PMS) [4,5]. PMS is present in 50% of patients with Carney complex (CNC), characterized by spotty skin pigmentation, myxomas of the heart, skin, and breast, and endocrine tumors [5–7]. PMS is found sporadically in 55% of cases and is usually benign, but the malignant type tends to metastasize [8–10]. The female–male ratio of PMS was 1.4:1 while the mean age was 37 years [4]. They are found most frequently in the cervical and thoracic spine (46%), but can also arise in soft tissue, stomach, skin, liver, parotid gland, and heart [10–13]. CNC is diagnosed at a mean age of 22.5 years, with 63% of patients being female in the largest genotyped series of CNC cases [5,14]. Carney complex 1 (CNC1), an autosomal dominant multiple neoplasia syndrome, are typically the result of inactivating mutations in the PRKAR1A gene on chromosome 17q24, which codes for the type 1A regulatory subunit of protein kinase A [8]. A family history is missing in up to 35% of PRKAR1A mutation carriers. A recent study has compared melanotic schwannomas (MSs) with and without psammoma bodies and concluded that there were no significant differences. PRKAR1A expression was lost in 35% of MS cases providing

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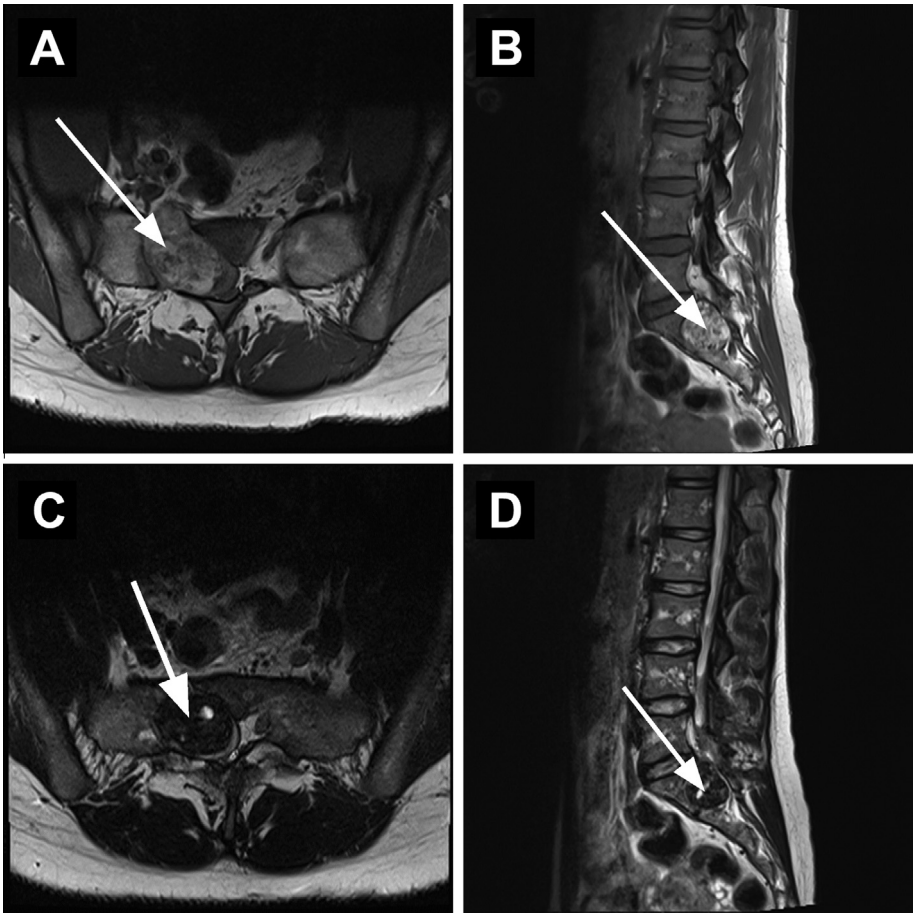

Fig. 1. MRI of lumbar spine (A) Axial T1-weighted, (B) Sagittal T1-weighted, (C) Axial T2-weighted, (D) Sagittal T2-weighted. The mass occupies the L5-S1 vertebrae. Arrows indicate position of the mass at the S1 neural foramen.

a link to CNC [15]. Compared to conventional schwannomas which are diffusely S100 protein positive, S100 was negative in 17% of MS cases [15]. The contrast with conventional schwannomas is highlighted by gene expression profiling, which show differentially expressed levels of >1700 genes [15].

The differential diagnosis of PMS includes melanomas and swchwannomas; however, neither contain adipose tissue or psammoma bodies [16]. In addition, the contrast between the high nuclear pleomorphism and low mitotic activity sets this tumor apart from melanoma, whereas the expression of melanocytic markers is useful in ruling out conventional schwannoma.

Although historically PMS have been considered variants of either schwannomas or melanocytic tumors, the differences on gene expression profile with either tumor suggest that PMS constitute a separate neoplasm [13]. In Carney's original study, all tumors that metastasized had enlarged nuclei with a huge nucleolus [5]. Mitotic figures were present in 20 of 40 tumors [5]. Both of these key features of a malignant PMS were present in our case. Abnormal mitotic activity (Fig. 2B), areas of necrosis (Fig. 2D), and enlarged nuclei (Fig. 2A) are consistent with Carney's original findings in PMS that metastasized. However, there is currently no reliable histopathological indicator of malignancy of PMSs [15,17]. Although pleomorphism and high mitotic activity is present in some metastasizing MSs, some have followed a benign course [17]. Conversely, some MSs with malignant behavior are histologically indistinguishable from benign tumors; and tumors with no mitotic activity or necrosis can metastasize. 24% of MS cases showed local recurrences, 44% showed metastases, and there is a disease-related mortality of up to 17% [12,15]. For these reasons, while MSs are generally considered benign variants of schwannoma, all occurrences should in fact be considered malignant.

We report a case in which we discuss findings that suggest aggressive behavior and report a number of newer molecular studies of PMS such as the test for BRAF V600E, a marker which is typically present in over 90% of melanomas, was not present in the patient's tumor [9,18]. This case of malignant PMS emphasizes the importance of making the correct diagnosis leading to the recognition of CNC and the uncertainty associated with the correct treatment in cases of malignant variety. Associated cardiac, thyroid, or other systemic manifestations may occur in the patient [10]. Prognosis is worst in incompletely excised tumors; thus, therapy in addition to total resection should always be attempted [5,12].

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.