Current Discoveries and Management of Psammomatous Melanotic Schwannoma

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Mini-review Article

ABSTRACT

Psammomatous melanotic schwannoma is a rare form of schwannoma that is distinct in terms of presentation, location, and nature compared to other types. This tumor is highly associated with Carney complex, but has also been seen in the neurofibromatosis syndromes. Although discovered over 80 years ago, official management guidelines have not been established. The following review comprises the current understanding of this rare tumor including genetic associations, presentation, imaging, pathology, prognosis, and management.

1. INTRODUCTION

The first case of melanotic schwannoma was described by Millar in 1932. The description used was "malignant melanotic tumor of the ganglion cells arising from the thoracic sympathetic ganglion" [1]. Psammoma bodies in schwannomas were then described by Kepes

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and Kernohan in 1959 [2]. In 1987, Danoff et al. [3] reported the common association of the melanocytic schwannomas with Carney complex. The description of "psammomatous melanotic schwannoma" (PMS) was established by Carney in 1990 when he removed the tumor from the posterior spinal nerve roots [4]. Fewer than 200 cases have been reported [5].

Typical schwannomas commonly occur in the central nervous system and follow a benign nature. They are associated with neurofibromatosis type I and II. Unlike the common schwannomas, PMS are prone to local recurrence and have metastatic potential [4]. These tumors are more associated with Carney complex, although some cases have been discovered in neurofibromatosis patients [6].

2. GENETIC ASSOCIATIONS

Fifty to fifty-five percent of PMS cases are associated with Carney complex (CNC), [4,7-9] an autosomal dominant genetic disease where there is a mutation within chromosome 17 affecting the PRKAR1A gene [10]. CNC presents with multiple lesions, including spotty pigmentation of the skin, cardiac myxomas, primary pigmented nodular adrenocortical disease, thyroid adenomas, and other lesions. Diagnosis of CNC requires at least two features of CNC [11,12]. Mice models have shown that PRKAR1A haploinsufficiency results in tumor formations in cAMP-responsive tissues, producing nonpigmented schwannomas as well as bone lesions and thyroid neoplasms [13,14].

PMS may signify a severe form of CNC. Large deletions of the PRKAR1A gene may induce the formation of PMS as well as various other characteristics of the complex. One case reports a large deletion on the gene which eliminated exon 3 of PRKAR1A. This led to the formation of a shorter protein lacking the capabilities to bind cyclic AMP and therefore activate protein kinase A [15,16].

Another genetic disease where PMS can arise is neurofibromatosis type I. Differing from Carney complex, neurofibromatosis type I is characterized by neurofibromas and café au lait spots. Both genetic disorders have mutations on chromosome 17. However, neurofibromatosis type I has the mutation on the 17q11 while Carney complex has the anomaly on the PRKAR1A gene (17q24) [17]. Most of the schwannoma tumors found in neurofibromatosis

are not PMS. Schwannomas that arise in the central nervous system under neurofibromatosis or familial schwannomatosis syndromes tend to be benign without pigmentation, calcification, or multicentricity [4,18-20].

3. PRESENTATION

The average age of PMS presentation is 33.2 years. However, if associated with Carney complex, presentation is earlier at 22.5 years average [4]. Females tend to be more affected than males, with a ratio of 1.4:1 [21,22]. PMS in Carney complex commonly arises in the spinal nerve roots, trigeminal nerve, gastric nerve plexuses, and sympathetic nerve chains [4,8,12,19,23-25]. Twenty-eight percent of cases present in spinal nerve roots while another 28% present near the GI tract (esophagus, stomach, rectum) [26]. Other locations that have been reported include the dermis, bone, parotid, and bronchus [8,25,27-34]. One case described a patient acquiring the neoplasm in five sites [4].

Symptoms are related to the location of the tumor. Symptoms suggestive of involvement of spinal nerves or other nerves are seen in 35.5% of patients. This includes motor and sensory abnormalities. Mechanical dysfunction of adjacent organs due to mass effect (i.e. stomach, heart) is seen in 13% of cases. Compression of the bronchi causing respiratory disturbances is observed in 6.5% of cases. The tumor is palpable in 12%. Cutaneous PMS manifests features similar to melanomas. Subcutaneous PMS present in a pattern similar to a slowly growing soft-tissue mass [35]. According to a review of 77 cases reported up to 1999, delay of diagnosis averaged at 3.6 years [36]. Pain is rarely noted. PMS growing on bone usually presents as pain along with a bony mass [37]. Asymptomatic presentations are noted in 29% of cases [4].

4. IMAGING

Imaging proves useful in the diagnosis and management of PMS. When originating from spinal nerves, radiographs and CT scans show enlargement of the intervertebral foramina and bone erosion and sclerosis. PMS on the spine is described as a soft-tissue tumor with "dumbbell" morphology [38]. Myelograms further depict obstruction of the contrast flow without displacement of the spinal cord [4]. Tumors making contact with bone show cortical erosion, sclerosis, and local destruction. For example,

PMS on the nerves of the chest wall tend to involve adjacent ribs and present with a calcified soft tissue mass surrounded by osteolytic and osteosclerotic areas [38]. The PMS tumor demonstrates bright densities within the soft tissue with a circumferential rim of sclerosis on radiographs. However, these imaging findings are not consistent among all cases [4]. The stomach and heart present with filling defects whenever the PMS tumor is in close proximity and causing intraluminal protrusion [4]. In asymptomatic patients, routine chest x-rays, physical exam, or surgeries incidentally find PMS tumors. Asymptomatic tumors were commonly found in the gastric proximity, although other cases have reported rectum, esophagus, and chest wall involvement [4].

5. PATHOLOGICAL FEATURES

A round-to-ovoid, melanin-containing tumor found on peripheral nervous tissue on gross examination is highly suggestive of PMS [2338]. The sizes ranged from 0.5 cm to 25 x 20 x 12 cm; most PMS are greater than 5 cm in diameter. Although not frequent, a thick, fibrous, occasionally pigmented capsule may encase these tumors. Within the tumor, pigmentation is scattered lacking any clear pattern. Although most tumors are solid, cysts can be found on the surface of the tumor [4,23,38]. Minor components of adipose metaplasia are scattered within the tumor [34]. The numerous blood vessels are thin-walled and sinusoidal. Significant hemorrhage can be present in tissue sections, characterized by accumulations of hemosiderin-laden macrophages [4].

Histologically, the tumor commonly is comprised of weakly eosinophilic, fusiform cells arranged in fascicles or bundles with different levels of cellularity. Nuclei are large, pale, and fusiform. Small, apparent nucleoli are seen within the nuclei. Bi-nucleated and tri-nucleated cells are commonly scattered within the tissue. Mitotic figures are also common, but are sparse in tissue samples [4,23]. The cytoplasm typically exhibits granularity via periodic acid Schiff (PAS) staining. Occasionally, the cytoplasm can be deeply eosinophilic, vacuolated, or clear [4]. Granules of coarse or fine brown pigment can be found around the tissue. These pigments are not reactive to Prussian-blue staining. Macrophages containing melanin with occasional lymphocytic infiltration are also reported. Mitotic bodies are also present, suggesting malignancy [23].

Psammoma bodies are found in 40-50% of melanotic schwannoma cases [39]. These bodies are PAS-positive and laminated. By definition, they are comprised of calcified swirls. They can range from being rarely to abundantly seen throughout the tissue section. Tumor cells typically are adjacent to the border of the bodies, but there are occasional instances where a well-defined halo separates the layers. Multinucleated giant cells are also occasionally noted within the psammoma bodies. These psammoma bodies differ from those seen in other tumors (e.g. meningioma) in that they tend to be large and coalesced [4].

The tumor can be labeled with antibodies directed towards S-100 protein, HMB-45, and vimentin in 95%, 95%, and 93% of cases, respectively [4,7,8,23]. Immunoreactivity is patchy rather than diffuse for HMB 45, melan A, and tyrosinase [34]. No tumors exhibited glial fibrillary acidic protein (GFAP), actin, and cytokeratin [4,8]. The neural crest cell ancestry accounts for the presence of these features and its similarities to melanocytes [7].

Electron microscopy shows cells connected via scattered simple junctions. Long strands of collagen exist between cells. Premelanosomes and melanosomes are present within the tumor cells. This presentation suggests that the origin of the pigmentation is from the tumor Schwann cells themselves rather than melanocytes [4,8,40,41]. Ultrastructural examination shows reduplication of the basal lamina, further suggesting Schwann cell-origin rather than a melanocytic derivative [8,23].

PMS is difficult to distinguish from primary melanocytic lesions. Histological presence of basement membrane material (i.e. reticulin and collagen IV), psammoma bodies, and adipose-like cells help differentiate the two entities in favor of PMS [8,34,35]. Also helpful is the use of mutational analysis for GNAQ codon 209 mutations. These mutations are highly specific for leptomeningeal melanocytic tumors [42].

Metastases from PMS occur in 13-15% of cases [7,36]. Metastases are found primarily in the lung and pleura, but can also been seen in the mediastinum, diaphragm, pericardium, endocardium, bone, liver, and spleen [4]. When malignant, PMS is a known cause of death in CNC. PMS appears in 10% of CNC cases, [43] and the rate of change to malignancy is 12% [4,12,24,25,44]. Death via metastatic disease is

the second most common cause of death (25% of deaths in CNC) after cardiac-related causes [12]. PMS is the most common cause of death via malignancy, contributing to 14% of deaths in CNC patients [44].

6. PROGNOSIS AND CURRENT MANAGEMENT RECOMMENDATIONS

About 10% of PMS tumors are malignant; [17] however, attempts of removal are indicated with all PMS tumors. Studies suggest that achieving long-term survival in PMS is difficult due to its aggressiveness and recurrence rate even several years post-operatively. Current treatment suggestions include a radical tumor extirpation in order to prevent recurrence [4,17,45]. Carney et al. [4] described 21 of 31 patients (67.7%) to be free from recurrent or metastatic PMS after 20-year follow-up. Successful outcomes are dependent on the grade of malignancy, bone metastasis, and visceral metastasis [46]. The Tomita prognostic score can be useful for PMS vertebral tumors [21,46]. Poor prognosis is associated with PMS arising from cranial nerves and those that were incompletely removed [6,31].

Another form of therapy is with radiosurgery, namely gamma knife surgery. Radiosurgery has proven effective for small- and medium-sized trigeminal schwannomas [47,48]. Pan et al. [49] found that 88.5% of tumors smaller than 30 mm shrank more than one-third in diameter after radiosurgery. They concluded that although complete resection is the ideal treatment, reduction in size serves as a suitable alternative due to its low morbidity [47,49].

Guidelines for adjuvant therapies have not been officially implemented. Mees et al. [17] performed adjuvant radiotherapy after surgery to further minimize the recurrence of PMS. After a 24-month follow-up, no recurrence had developed. Greater than 5-year follow-up is recommended for all PMS survivors. However, adjuvant radiation therapy has not shown a clear and definite benefit. Although fractional radiation therapy can be employed for difficult PMS tumors, including those near vital structures such as the spinal cord, adjuvant therapy has yet to show a definite mortality benefit [26].

The use of chemotherapeutic drugs has scarcely been studied. Ifosfamide and doxorubicin have been reported to be the most effective in treating PMS [35,50]. Steins et al. [50] also report partial remission in two cases that used carboplatin and etoposide. However, chemotherapy has shown low response rates with no mortality benefit [26].

Due to recurrences being documented up to 5 years, follow-up is necessary [47,51]. Local recurrence rate is 15-35% and metastatic spread is 26-44% within 5 years [5,8,36] and 72% of metastatic outcomes were discovered in less than 4 years [5]. Recurrences are due to tumor invasion into adjacent tissue with difficult or incomplete resections, and are less frequent when PMS presents in soft tissue due to ease of complete resection [7]. The most common area of metastasis is the lung. Although most cases of PMS are benign, there are no definitive histological findings that suggest a malignant nature [7,31,47]. The only indications of malignancy are the basic histological features, including eosinophilic and violaceous marconucleoli, pleomorphism, and increased mitotic bodies [8,47]. A mitotic rate of greater than 2/10 HPF has been statistically correlated with metastases (p=0.008) [5]. Due to these findings, careful imaging follow-up, such as with MRI, of the primary location and the lungs is recommended in patients with surgically resected PMS [26,52].

When PMS is diagnosed, a search for other diagnostic findings of CNC should be undertaken [6]. Diagnosis of CNC will allow for appropriate management of serial echocardiograms and other necessary biochemical or imaging surveillances. Family screening for the genetic disorder may also be required. Cardiovascular complications are the most common cause of morbidity and mortality of CNC while tumor metastasis remains second; PMS is the most common tumor to metastasize. Therefore, early observation and management of the cardiovascular disorders is necessary when CNC is suspected [11].

7. CONCLUSION

Psammomatous melanotic schwannoma is a rare tumor that typically presents within unique cases of Carney complex. Different from usual schwannomas, PMS presents adjacent to the spinal cord and nerve roots, esophagus, and stomach in addition to other locations. While the treatment of PMS is not official, resection of the tumor has shown 20-year remission rate of 67%. Despite no clear benefit with neoadjuvant therapy, it is still urged to employ chemotherapy and radiation in all cases. Nevertheless, PMS is a rare disease that requires further

understanding in terms of presentation and therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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