Angiosarcoma Developing in a Vagal Schwannoma: A Rare Case Report

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Abstract Angiosarcoma arising in a schwannoma is extremely rare with only fourteen cases having been reported in the literature to the best of our knowledge. Amongst these fourteen, only five cases developed from vagal schwannoma. We describe a case of epithelioid angiosarcoma arising in a long standing vagal schwannoma in a 41 years male patient. Grossly the tumor was well encapsulated with variegated cut surface. On microscopy the tumor had two distinct components composed of benign schwannoma and malignant angiosarcoma which were further confirmed by immunohistochemistry. On further work up, he was found to have multiple distant metastases. This is the sixth reported case of angiosarcoma arising in a vagal schwannoma. The proposed histogenesis of this rare transformation, its prognostic factors and a review of literature regarding this entity is discussed.

Keywords Angiosarcoma · Immunohistochemistry · Schwannoma · Vagus nerve

Introduction

Schwannomas are slowly growing benign nerve sheath tumors composed entirely of well differentiated schwann cells which are neuroectodermal in origin. Degenerative changes are often seen in long standing cases of

schwannoma but they rarely undergo malignant transformation, and if so, most often as malignant peripheral nerve sheath tumors (MPNST) and extremely rarely as angiosarcomas [1]. On the other hand, angiosarcomas arising from peripheral nerve sheath tumors are also rare. They may develop in neurofibromas in the setting of neurofibromatosis 1 (NF 1), however, development of angiosarcoma in cases of schwannoma is least common with only numbered such cases reported so far [2]. Here we discuss a case of angiosarcoma arising in a long standing vagal schwannoma in an adult male patient, with distant metastases.

Case Report

A 41 years old male presented with a swelling on the left side of the neck for 12 years. It was insidious in onset and gradually progressive. Initially the swelling was present in the left submandibular region and was approximately the size of a pea. It gradually progressed over the years, with rapid increase in size for last 2 months. There was no history of pain associated with it, but there was history of difficulty in swallowing and change in character of voice (hot potato voice). There was no history of fever, any other complaints, or any other swelling over the body. Patient underwent tonsillectomy in 2002. Personal and family histories were not significant. General physical examination and systemic examination of cardiovascular, respiratory, per abdominal, and central nervous systems were within normal limits. On local examination, there was a single, mobile, non-tender, firm, nodular swelling of approximately 10 × 8 cm size on left side of neck, extending superiorly to mandibular ramus, anteriorly up to midline, posteriorly to posterior border of sternocleidomastoid muscle and inferiorly three fingers above the clavicle. In oral cavity, bulge was seen in the left tonsillar fossa pushing

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Fig. 1 MRI with contrast: image showing a well defined heterogeneously enhancing soft tissue mass in left parapharyngeal space with hemorrhage

the anterior pillar medially. Pre and post contrast magnetic resonance image (MRI) of the neck revealed a large soft tissue mass lying in the left parapharyngeal space measuring approximately $11.5 \times 6.9 \times 6.7$ cm in size. Significant blooming artefacts were noted within it on the gradient images suggestive of haemorrhages (Fig. 1). It was extending inferiorly into the submandibular and carotid spaces displacing the

common carotid, internal and external carotid arteries anteriorly. Radiologically, the possibilities of paraganglioma/schwannoma were suggested. Subsequently on fine needle aspiration (FNA), the aspirate was hemorrhagic and showed few large tumor cells with pleomorphic nuclei, prominent nucleoli, and abundant cytoplasm. On FNAC (fine needle aspiration cytology), the morphological possibilities of paraganglioma or a malignant tumor were given. Considering the radiological and cytological possibilities, extracranial skull base resection was done. Intraoperatively the mass was found to be originating from the left vagus nerve and was adherent to the common carotid artery. During surgery the left vagus nerve was sacrificed.

Pathological Findings

Grossly, the mass was well encapsulated and measured $11 \times 6.5 \times 3.5$ cm. Cut surface showed variegated appearance with peripheral 1/3rd portion showing grey white, solid firm areas having gelatinous appearance while rest of the mass showed areas of haemorrhage, necrosis, and cystic change (Fig. 2). Microscopic examination showed two types of tumor components. The peripheral areas showed features of a benign nerve sheath tumor which was composed of hypercellular Antoni A areas with characteristic Verocay bodies, admixed with hypocellular Antoni B areas, diagnostic of schwannoma (Fig. 3). Admixed with this benign component was a second tumor component, situated mainly centrally but extending peripherally also. It was composed of numerous anastomosing vascular spaces of variable size lined with large atypical and highly

Fig. 2 Gross photographs showing a well encapsulated mass (a), cut surface showing grey white gelatinous areas at the periphery, and rest of the mass showing hemorrhage, necrosis and cystic change (b)

Fig. 3 Well encapsulated spindle cell tumor with hypercellular Antoni A areas (*inset* Verocay bodies) (**a**), and hypocellular Antoni B areas (**b**) (H&E $\times 10$)

Fig. 4 Anastomosing vascular spaces lined with atypical endothelial cells (**a** $\times 10$), epithelioid morphology and increased mitotic activity with some atypical mitoses (**b** $\times 40$) (H&E)

pleomorphic epithelioid cells having moderate amount of eosinophilic cytoplasm, vesicular nuclei, and prominent eosinophilic nucleoli. Within some channels, papillae lined by atypical cells were also observed. The epithelioid cells showed increased mitotic activity with occasional atypical mitoses (Fig. 4). There were large areas of necrosis and haemorrhage. Few medium sized blood vessels showed thrombotic occlusion. The tumor was focally infiltrating the capsule. On immunohistochemistry (IHC), schwann cells were positive for S100 and showed low proliferative activity (Ki 67 = 1–2 %); while the vasoformative tumor cells were positive for CD31, and were negative for CD34 and S100. They showed high proliferative activity (Ki 67 = 40–50 %) (Fig. 5). Final results of IHC studies are tabulated (Table 1). Thus a final diagnosis of epithelioid

angiosarcoma arising in benign schwannoma was made. Following this, positron emission tomography (PET) scan of the patient was done which revealed FDG avid, ill defined soft tissue mass lesion in the left parapharyngeal region likely representing the residual disease with local infiltration into the basi-occiput. A few mildly FDG avid, left cervical lymph nodes, FDG avid hypodense lesion in the liver, FDG avid, osteolytic skeletal lesions and extensive mildly FDG avid and non FDG avid bilateral pulmonary nodules, likely metastatic were noted along with moderate ascites. The subsequent liver biopsy showed metastatic angiosarcoma (Fig. 6). Patient was put on chemotherapy (Ifosfamide + Adriamycin + Dexamethasone). He received two cycles of the same. The patient died after 4 months due to complications of widespread metastases.

Fig. 5 IHC (a–f) S100—schwann cells show positivity (a) while atypical endothelial cells are negative for S100 (b). CD 31—atypical endothelial cells show positivity (c) while schwann cells are negative for CD 31 (d). Ki 67—atypical endothelial cells show high proliferative activity—40–50 % (e) while schwann cells show low proliferative activity—1–2 % (f)

Discussion

Schwannomas are usually sporadic and solitary but multiple schwannomas are seen in association with neurofibromatosis type 2 (NF 2) or schwannomatosis. They can be intracranial or peripheral. Peripheral schwannomas most commonly involve head and neck region or flexor aspect of extremities. The peak incidence is in the second to fifth decade of life. Clinically they can be incidental or can present with asymptomatic swellings or with pain and symptoms of nerve root compression. Macroscopically, they are usually well encapsulated tumors with light tan and glistening cut surface. In cases of peripheral tumors, nerve of origin can be attached eccentrically to the tumor in most cases. Microscopically, it shows characteristic

Table 1 The results of immunohistochemical studies

Antibodies	Source	Dilution	Reactivity	
			Schwann cells	Epithelioid cells
S100	Dako	Prediluted	+	—
CD 31	Cell mark	Prediluted	—	+
CD 34	Biogenex	Prediluted	—	—
Ki 67	Biogenex	Prediluted	1–2 %	40–50 %

hypercellular Antoni A and hypocellular Antoni B areas along with presence of Verocay bodies. Cellular, melanotic and plexiform are different variants of this tumor. On IHC,

Fig. 6 PET CT scan showing residual disease in left lateral neck (a), FDG avid lesion in the liver (b), metastatic angiosarcoma in the liver (c H&E $\times 10$), and tumor cells showing positive staining for CD 31 (d)

Schwann cells strongly and diffusely express S100. On genetic analysis most of the schwannomas show mutation in NF 2 gene on chromosome 22 which is a tumor suppressor gene and encodes a protein called merlin. Schwannomas are slow growing benign tumors. Long standing cases often undergo degenerations but these tumors rarely undergo malignant transformation [3].

McMenamin and Fletcher reviewed 17 cases of schwannoma with evidence of malignant change. They noted microscopic collections of epithelioid cells in schwannomas and suggested that these represent an early stage of malignant transformation. Amongst the 17 cases, nine were labelled as epithelioid malignant change and four cases each of epithelioid malignant peripheral nerve sheath tumor (EMPNST) and angiosarcoma were described [1]. Woodruff et al. [4] analysed nine cases of malignant transformation in schwannoma and found that malignant component differed morphologically from that of conventional MPNST. It is characterized by epithelioid differentiation rather than spindle cell morphology. Seven out of nine cases had epithelioid morphology while in two cases

malignant component had neuroepithelial differentiation. However, exact categorization of the malignant component was not done in all cases. No explanation was given in either of the studies regarding the propensity of epithelioid morphology in malignant component of schwannoma.

The first case of angiosarcoma arising in a sciatic nerve schwannoma was described by Trassard et al. [5]. To date, only 14 such cases are described in the literature (Table 2) (1, 2, 5–10). No case is found to be associated with NF 1/2 or schwannomatosis. All cases have been reported in sporadic schwannomas. Amongst the 14 cases, only 5 cases of angiosarcoma developed in a schwannoma arising from vagus nerve in the neck. These presented in the age group of 50–74 years with the mean age of 63 years and showed male predominance. Grossly, the size ranged from 2.5 to 6 cm. Right neck involvement was far more common than the left [10]. Patients in such a scenario usually present with pain or rapid increase in the size of pre-existing lesion [1]. The present case occurred in a relatively younger age with larger tumour size as compared to the previously reported cases. It presented with rapid enlargement of the pre-existing long standing swelling.

Table 2 Reported cases of epithelioid angiosarcoma arising in schwannoma

Sr no.	Case	Age (year)	Sex	Size (cm)	Location	Treatment	Outcome
(1)	Trassard et al. [5]	65	M	6	Rt thigh sciatic nerve	Surgery + RT + CH	No disease
(2a)	Mentzel and Kantenkamp [2]	73	F	5.5	Rt neck vagus nerve	Surgery	No disease
(2b)		63	M	4	Rt neck vagus nerve	Surgery + RT	Death with disease
(3)	Rückert et al. [6]	50	M	4.5	Rt neck vagus nerve	Surgery	Distant metastasis
(4a)	McMenamin and Fletcher [1]	74	F	5.5	Rt neck vagus nerve	Surgery	No disease
(4b)		40	F	2.5	Rt thigh sciatic nerve	Surgery	No disease
(4c)		17	F	6	Rt neck phrenic nerve	Surgery + RT + CH	Distant metastasis, death
(4d)		39	F	7.8	Rt buttock	Surgery	Unknown
(5)	Shundo et al. [7]	68	F	Uk	Rt chest	Surgery	Death with disease
(6)	Ito et al. [8]	66	M	Uk	Intracranial vestibular nerve	Surgery	Death with disease
(7)	Lee et al. [9]	73	M	30	Lt thigh sciatic nerve	Surgery	Distant metastasis
(8a)	Li et al. [10]	67	M	11	Rt abdominal adrenergic nerve	Surgery	No disease
(8b)		38	M	7	Rt inguinal sciatic nerve	Surgery + RT	Distant metastasis
(8c)		55	M	6	Lt neck vagus nerve	Surgery	No disease

M male, *F* female, *Uk* unknown, *Rt* right, *Lt* left, *RT* radiotherapy, *CH* chemotherapy)

The histogenesis of angiosarcoma arising in a schwannoma remains unclear but various hypotheses have been proposed. Trassard et al. [5] suggested that angiosarcomas arise directly from the pre-existing vasculature of the schwannoma, and demonstrated Weibel-Palade bodies in the cytoplasm of epithelioid tumor cells by electron microscopy in support of this hypothesis. Rückert et al. [6] proposed that chronic vascular stasis and edema in long standing cases of schwannoma are implicated in the pathogenesis of angiosarcoma similar to lymphedema associated angiosarcoma. The role of angiogenic factors in development of angiosarcoma in schwannoma is uncertain. But Mentzel et al. [2] found positive staining for vascular endothelial growth factor (an angiogenic factor) in the Schwann cells in one such case and suggested the importance of angiogenic factors in the development of angiosarcoma.

The important differential diagnoses for such cases include EMPNST and variants of schwannoma such as ancient, cellular, and epithelioid type. EMPNST is malignant transformation of schwann cells characterized by epithelioid cells growing in sheets, forming nodules or singly dispersed, with features of malignancy in the form of nuclear pleomorphism, prominent nucleoli, and increased mitoses [1]. Ancient schwannoma represents degenerative changes in long standing cases. It can be associated with cellular atypia of schwann cells along with changes such as haemorrhage, hemosiderin laden macrophages, calcification, cystic degeneration and hyalinization. Furthermore, angiosarcoma and ancient changes can coexist in the same tumor. Cellular schwannoma is composed exclusively of

Antoni A areas. Mitotic activity can be seen in such cases. Epithelioid schwannoma consists predominantly of epithelioid cells which are round cells with occasional intranuclear cytoplasmic inclusions. Both cellular and epithelioid schwannomas lack features of malignancy in the form of cellular atypia, hyperchromatism, high mitotic activity including atypical mitoses [11]. IHC is helpful for differential diagnosis in all entities. The tumor cells of EMPNST, ancient, cellular and epithelioid schwannoma are positive for S100, while malignant cells of angiosarcoma are usually positive for CD31 and CD34. Factor VIII (von Willebrand factor), CD34 (human hematopoietic progenitor cell antigen) and CD31 (a platelet-endothelial cell adhesion molecule) are commonly used markers for endothelial differentiation. Factor VIII is the most specific marker but it is not sensitive. CD34 is expressed by many angiosarcomas; however, CD31 is more sensitive and specific antigen for endothelial differentiation [12, 13].

Angiosarcoma developing in a schwannoma or otherwise (de novo) carries an overall poor prognosis. As the malignant transformation of schwannoma to angiosarcoma is rare and the number of cases reported to date is limited, there is no established treatment protocol available in these cases. But as these tumors are known to have aggressive behaviour and harbour metastatic potential, wide local surgical resection followed by postoperative radiotherapy is thought to be the most appropriate management [6]. The 14 cases reported to date were found to have a bad clinical course on follow up. The average follow up duration was 31 months (with a range of 10 days–90 months). Four patients had distant metastasis while 4 died of the disease

[10]. Epithelioid morphology, incomplete resection, penetration of the capsule with infiltration of the surrounding soft tissues, and large tumor size are predicted to be associated with worse prognosis [10].

Conclusion

Although malignant change in a schwannoma is a rare event, it can transform into a malignancy, usually in the form of EMPNST or rarely as angiosarcoma. The symptoms of pain or rapid enlargement in a long standing case should never be ignored as they can be an early indicator of malignant change and such patients require prompt management as these malignant transformations carry a very poor prognosis. The morphology and IHC are extremely useful tools in such cases to arrive at a diagnosis.

Conflict of interest The authors declare that there are no conflicts of interest.

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