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Review Article

Malignant Glomus tumour of the head and neck–A review

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ABSTRACT

Malignant glomus tumors are rare tumors of mesenchymal origin arising from the smooth muscle cells of the glomus body. A vast majority of the glomus tumors are benign and are commonly found in the distal extremities. Occasionally, malignant variant of glomus tumours present with a large size, infiltrative growth pattern, aggressive biological behavior such as recurrences, wide spread metastases and even death in some instances. Malignant Glomus tumors were believed to be low grade malignancies. However, from subsequently reported cases it has been evident that 38% of the MGTs have lead to fatal metastases. Malignant Glomus tumors have been reported in other organ sites like mediastinum, kidney, lungs, however their occurrence in the head and neck region is rare. This review discusses in detail about this rare but important soft tissue neoplasm.

1. Introduction

Malignant glomus tumors are rare tumors of mesenchymal origin arising from the smooth muscle cells of the glomus body [1,2]. A vast majority of the glomus tumors are benign and are commonly found in the distal extremities [3]. Occasionally, malignant variant of glomus tumours present with a large size, infiltrative growth pattern, aggressive biological behavior such as recurrences, wide spread metastases and even death in some instances [1,5–8]. First reported by Lumley and Stansfeld [10] in 1972, Malignant Glomus tumors were believed to be low grade malignancies. However, from subsequently reported cases [1,3,10,11] it has been evident that 38% of the MGTs have lead to fatal metastases.

Glomus tumors comprise only 2% of the soft tissue neoplasms and the occurrence of a Malignant Glomus tumour is even rarer. Malignant Glomus tumors have been reported in other organ sites like mediastinum [8], kidney [12], lungs [13], however their occurrence in the head and neck region is rare. In the head and neck region, 14 cases of MGTs have been reported [15] with one case occurring in the oral cavity [8]. Among the reported cases, 3 are pediatric Malignant glomus tumors [14–16]. Though a rare neoplasm, MGTs have a relatively aggressively behavior resulting in fatal metastases and death. This emphasizes the importance of an accurate diagnosis of this rare entity on histopathological grounds amongst the various round and spindle cell neoplasms involving the oral and maxillofacial region.

2. History

Glomus body or Sucquet- Hoyer Canal is intimately associated with the blood vessels around arteriovenous anastamoses and plays a role in blood flow and thermoregulation [7]. Glomus cell, as first described by Masson [16] is a cuboidal cell with an eosinophilic cytoplasm and centrally placed rounded vesicular nucleus with myoid differentiation. The glomus cells are arranged in layers around the narrow endothelial lined vessels of the arteriovenous anastamoses [16]. Malignant Glomus tumour is a rare entity. Lumley and Stansfeld first reported a case of atypical locally infiltrating glomus tumour in 1972 [9]. The first case report of Glomus tumour with extensive metastases was that of Brathwaite and Poppiti [1] followed by Watanabe et al [17]. In the head and neck region six cases of Malignant glomus tumors with distant metastases have been reported [1,4,14,18–20].

3. Clinical features

GTs occur in a wide age group from 2 years [14] to 78 years [6]. Generally, the incidence of malignant Glomus tumour is rare in children. Two pediatric MGTs were reported in a 2 year old and 6 year old. In the case series of MGTs reported by Folpe et al one patient was a

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Table 1
Clinical Findings of reported cases of Pediatric Malignant Glomus Tumours.

case No	Author	Age	Gender	Site	Recurrence	Metastatic Site	Time to Metastases
1	Folpe et al	9	F	Lung	No	Small Bowel	5 years
2	Wolter et al	2	M	Neck invading common carotid	No	Lung	At time of presentation
3	Grampurohit et al	6	F	Neck Mass	No	No	N/A

9 year old child. (Table 1) Clinically, the patients present with superficial or deep seated lesions and symptoms related to compression or infiltration into the adjacent anatomic structures. Glomus tumors have been reported in sites which do not normally contain the glomus body. Metastases at the time of presentation has been reported in many cases of Malignant Glomus tumours [3]. Among the 32 cases reported by folpe et al 3 patients presented with a recurrence between 3–5 years [3].

4. Histopathology

Histopathologically, Glomus tumors are composed of monotonous sheets of small round cells with eosinophilic cytoplasm, central round nuclei and distinct cell borders. The cells are arranged around small blood vessels.

The first attempt to classify MGTs or atypical Glomus tumors were by Gould et al [7]. They categorized these tumors under three categories i) locally infiltrative glomus tumor - tumors that are cytologically bland tumors with infiltrative growth pattern ii) glomangiosarcoma arising in a benign glomus- cytologically malignant tumor arising in a readily identifiable glomus tumor iii) glomangiosarcoma de novo for malignant appearing tumors without identifiable benign glomus areas.

Folpe et al proposed a classification of Glomus tumors with atypic as follows i) malignant glomus tumor, ii) Symplastic glomus tumor-glomus tumour with nuclear atypia only (iii) glomus tumor of uncertain malignant potential, and iv) glomangiomatosis (histologically benign glomus tumor with diffuse growth). They proposed that the term “Malignant Glomus Tumour” be designated only to lesions fulfilling one of the following criteria i) deep location and size more than 2 cm, ii) atypical mitotic figures, iii) marked nuclear atypia and mitotic activity (5 mitoses/50 HPF). In the present case, the tumour was intra osseous, > 2 cm in size, locally recurrent, with nuclear atypia and mitotic activity [3].

There are two proposed ways for the evolution of MGT i) evolution from a pre existing glomus or symplastic gloms tumour or ii) MGTs arising de novo.

The sine qua non in the diagnosis of Malignant Glomus tumours is the identification of the key histologic features namely sheets of round cells with scanty cytoplasm, rounded nucleus, distinct cell borders, branching capillary vasculature, perivascular arrangement of tumour cells.

5. Differential diagnosis

The spectrum of lesions that come under the differential diagnosis for this microscopic picture in the current site were Ewing sarcoma/ primitive neuroectodermal tumour, neuroblastoma, rhabdomyosarcoma, lymphomas, hemangiopericytomas and synovial sarcoma.

Ewing Sarcoma/ PNET is characterized by monotonous population of round blue cells with scant eosinophilic cytoplasm. Homer Wright Rosettes and pseudo rosettes may be seen. The tumour is composed of slit like capillaries.They also have PAS demonstrable intracytoplsmic glycogen. The tumour cells are immunoreactive with Neuron Specific Enolase and other neuroectodermal markers like S100 and synaptophysin. The nuance of diagnostic significance here is that only PNET reacts with neuroectodermal markers whereas “pure” Ewing Sarcoma shows no neural differentiation on histological sections, immunohistochemistry or electron microscopy. CD 99 is a cell surface glycoprotein that shows diffuse membranous staining in 95% of ES/ PNET. However CD 99 is not very specific, as it is also expressed by other tumors included in the differential like lymphoblastic lymphoma (> 90%) and rarely rhabdomyosarcoma. FLI expression is seen in 70% of the Ewing Sarcoma, but shows significant cross reactivity with lymphoblastic leukemia, non Hodgkin’s lymphoma and endothelial cells. Hence, it is mandatory that these markers are interpreted in context with the results of the other markers in identifying the lineage [21].

Neuroblastomas are composed of small round cells in a prominent background of capillaries and are supported by a characteristic Neurofibrillary matrix. A high grade neuroblastoma may show significant pleomorphism, marked mitotic activity and minimal to absent fibrillary matrix [22].

Lymphomas are histologically characterized by a diffuse population of highly pleomorphic cells, with not so abundant cytoplasm, and occasional areas of spindling. It also has a significant morphological and immunohistochemical overlap with Ewing Sarcoma. Immunohistochemically, almost all lymphomas other than lymphoblastic lymphoma are positive for the Leukocyte Common Antigen CD 45 [23].

Embryonal rhabdomyosarcoma histologically presents with small to medium sized, round undifferentiated cells showing nuclear atypia. The key marker that aids in the diagnosis of this neoplasm is desmin. Desmin is typically expressed in skeletal muscle and smooth muscle except some vascular smooth muscle. It plays a significant role in identifying tumors with skeletal muscle differentiation on immunohistochemical grounds [24]. Desmin can immunohistochemically alert a diagnosis of rhabdomyosarcoma even in a tumour with an unusual histopathological picture. Rhabdomyosarcomas are notorious for their aberrant expression of many antibodies and require careful interpretation.

6. Proposed pathogenesis

Recent Studies have thrown significant insight into the cell of origin and pathogenesis of Malignant Glomus tumour especially in sites where they are normally absent. Their possible origin from pericyte has been long proposed. This is further supported by the fact that RGS5, regulator of G-protein signaling 5 a novel pericyte marker is robustly expressed in pericytes [25]. This marker is also expressed across all benign and malignant glomus tumours establishing a pericytic lineage of glomus cells. It is also suggested that there is a novel MIR143-NOTCH fusions in glomus tumours causing an aberrant activation of Notch pathway. The stage dependent expression of MiR 143/MiR 145 elicits a critical switch for phenotypic modulation of the vascular smooth muscle cells [26]. MIR143 is a strong promoter within the smooth muscle lineage and on translocation may cause NOTCH overexpression. Notch signaling plays a significant role in developing and adult vasculature. This rearrangement seen in Malignant glomus tumour irrespective of the anatomical site of the tumour. This demarcates them distinctly from other pericytic tumours though they share the same antigenic expression. Recent studies have also proposed a SMARCB1 inactivation driven oncogenesis in Malignant glomus tumour especially in the case of a recurrence [26]. SMARCB1 is a member of the SWI/SNF multisubunit chromatin remodeling complex that plays a fundamental

role in regulating transcription. It is expressed in normal cells. Inactivation of SMARCB1 has been observed in many other neoplasms including Malignant Rhabdoid tumor, Renal medullary carcinomas, 50% of epithelioid malignant peripheral nerve sheath tumors, extraskeletal myxoid chondrosarcomas, and poorly differntiated Chordomas. Though the exact mechanism of oncogenesis is not clear the authors propose a possibility of Cyclin D over expression secondary to SMARCB1 inactivation [26].

7. Conclusion

In conclusion, though malignant glomus tumors are rare in the head and neck region a proper knowledge of these neoplasms is essential for identification and appropriate management of these rare entities.

Conflict of Interest

None.

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