Glomus cells with discrete nuclei arranged in sheets and cords comprise the glomus cancer

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Abstract

Also known as glomangioma, glomangiomyoma, or glomangiomatosis, a glomus tumour is a benign, perivascular hamartoma that develops from the glomus apparatus or a mesenchymal neoplasm that is essentially made up of modified smooth muscle cells. Neurofibromatosis type 1 (NF1) bi-allelic inactivation can result in glomerus tumours that develop concurrently with the NF1 gene. Moreover, the RAS-MAPK pathway is activated when neurofibromin in glomus cells is decimated. There is a subungual, gradually progressive, slightly tinged, bluish-red papule that exhibits the classic triad of symptoms: localised sensitivity, pain when exposed to cold, and intense pain with mild trauma. Morphological analysis reveals a blend of smooth muscle cells, glomus cells, and prominent vascular features. The spheroid nuclei are punched out and surrounded by minimal cytoplasm. The stroma is amphophilic to eosinophilic, and the capillary-sized vasculature is circumscribed by branching.

Introduction

A rare type of benign perivascular hamartoma that arises from the glomus apparatus is called a glomus tumour. Glomus bodies make up the morphological composition of glomus tumours, which are typically less than 1 cm in size. Glomus bodies are typically found in efferent veins, arterioles, and anastomotic blood vessels. Modified glomus cells, which are specialised smooth muscle cells acting as chemoreceptors, give rise to glomus tumours. Glomus cells typically control vascular outflow in capillaries in response to internal and external temperature changes [1]. The glomus tumour is hypothesised to be a mesenchymal neoplasm primarily composed of smooth muscle cells that have undergone modification and arise from the glomus body.The majority of peripheral glomus tumours are benign, present with severe pain and tenderness, develop gradually, and can take time to detect because they are small. The rare malignant glomus tumour is deep, visceral, and massive, measuring more than 2 cm. An enormous intravenous glomus tumour may also develop. Glomagiosarcoma is another name for malignant glomus tumours [1,2]. Depending on its particular shape, glomus tumours may also be called glomangiomas, glomangiomyomas, or glomangiomatosis. Nonetheless, misnomers pertaining to specific sites, as glomus faciale, glomus jugulare, glomus tympanicum, or glomus vagale, are fundamentally suggestive of paragangliomas. The term "glomangiopericytoma" refers to a glomus tumour with a noticeable hemangiopericytic vasculature. However, the aforementioned tumours are not the same as sinonasal glomangiopericytoma or pericytic neoplasm, which are identified at particular locations [1,2].

Disease Characteristics

The globus tumour is a benign tumour that has an uncommonly dangerous form. Glomus tumours typically account for less than 2% of soft tissue neoplasms, with an estimated 1.6% of cases. Glomus tumours typically develop in adults between the ages of 20 and 40, peaking in the third or fifth decade and reflecting a corresponding gender predisposition. However, the subungual lesion shows a 3:1 ratio of female to male, indicating a preponderance of females. The spinal canal has never been implicated before, and glomus tumours can cause neurological symptoms that are so strong that they affect the spinal cord and nerve roots. Glomus tumours are often described as microscopic lesions on the hand or other distal extremities, particularly in the subungual area where glomus bodies are concentrated. Furthermore, Numerous locations, including the lung, stomach, pancreas, liver, gastrointestinal tract, and genitourinary tract, can develop glomus tumours [2, 3]. A malignant glomus tumour is identified by certain morphological characteristics, including abnormal mitotic figures, deep-seated tumefaction, and a tumour size greater than 2 cm, with increased neoplasia located in the paravertebral area or thoracic cavity.

Benign or atypical tumour tumefaction may be accompanied by vertebral dislocation, tumour expansion into the neighbouring spinal canal through an enlarged intervertebral foramen, and sporadic back discomfort. Severe clinical symptoms result from the tumor's ongoing progression. Magnetic Resonance Imaging (MRI) provides an example of spinal cord compression [3,4].

Disease Pathogenesis

Biallelic inactivation of the Neurofibromatosis type 1 (NF1) gene is typically the cause of glomerus tumours that express the NF1 gene concurrently. Moreover, the RAS-MAPK pathway is activated when neurofibromin in glomus cells is decimated. Mutations in the glomulin gene, which are frequently expressed in vascular smooth muscle cells, cause familial glomus tumours, which exhibit glomu-venous malformation [3, 4]. Certain cases may exhibit co-occurring genomic translocation and ensuing onco-genic NOTCH pathway activation, primarily due to translocation within the MIR143 promoter region. The glomus tumour is a specialised arteriovenous anastomotic formation that regulates heat within cutaneous surfaces. It is commonly derived from the Sucquet-Hoyer canal of the glomus body, and is identified by a layered circumscription of epithelioid glomus cells that are immune reactive to Smooth Muscle Antigen (SMA). In order to preserve body heat and control temperature, cold temperatures guarantee the relaxation of glomus cells in addition to patent vascular anastomosis, which reroutes vascular outflow within coherent capillary networks [2,4].

Clinical Elucidation

Tumefaction progresses gradually and presents with a subungual, bluish-red, slightly tinged papule along with the traditional triad of symptoms: localised sensitivity, pain when exposed to cold, and severe pain with mild trauma. A glomus tumour can be accurately identified by magnetic resonance imaging (MRI) if the clinical symptoms are relevant. A glomus tumour is primarily a cutaneous lesion that is often found on the subungual area of the finger, though it can occur anywhere. While glomus tumours can occur anywhere, the fingers (27%) and upper extremities (62%) are the most commonly implicated sites due to the prevalence of subungual lesions. The trunk wall (11%), internal locations (11%), lower extremities (9%), or head and neck (7%), are the adjacent sites that define glomus tumours. Unlike benign tumours, atypical and malignant types of glomus tumours are often deep-seated [4,5]. The symptoms of a glomus tumour include extraneously radiating pain paroxysms that are out of proportion to the size of the tumour. In addition to being brought on by changes in temperature or tactile stimulation,

pain can also be brought on by hypoesthesia, muscular atrophy, or osteoporosis. The NF1 gene is expressed in some glomus tumours that arise in the fingers and toes. There are lytic lesions and erosion in the implicated bone structures. Imaging investigations may misidentify deep-seated glomus tumours as paragangliomas or neurilemmomas, which can be difficult to distinguish [4,5].

Histological Elucidation

The single tumour is identified as a distinct, protruding, open, reddish-colored, and pigmented mass that contains small nerve fibres. The majority of superficial lesions have a size of less than 1.0 cm. An irregular, nodular, and hemorrhagic tumefaction is visible on the cut surface. Upon fine needle aspiration, there are foci of bleeding, sporadic inflammatory cells, and cohesive clusters and aggregates of round, uniform cells with little cytoplasm mixed in [4,5]. There are also scattered, amorphous, magenta-colored ground substance. A morphological combination of smooth muscle cells, glomus cells, and coherent vascular elements can be seen in glomus tumours. The cellular component has capillary-sized, branching vasculature encircling spheroid, punched-out nuclei surrounded by an amphophilic to eosinophilic stroma. Examples of this type of cell are diverse, spheroidal cells with individual, regular, round to ovoid nuclei that lack significant nuclear pleomorphism [4,5]. Atypical mitotic figures in conjunction with metastasis, observed in as many as 40% of cases, or considerable nuclear atypia and concomitant mitotic activity are characteristics of malignant metamorphoses of glomus tumours. Upon microscopic inspection, a well-defined nodule is observed, mostly consisting of smooth muscle cells, glomus cells, and coherent vasculature. The majority of cases (75%) are of the solid variety, in which the glomus tumour is primarily composed of glomus cells, insufficient vasculature, and few smooth muscle cells [5, 6]. An estimated 20% of cases are identified as glomangiomas, which are neoplasms with a mostly vascular component. An estimated 5% of patients have glomangiomyoma, which is defined as a cancer having a significant smooth muscle cell and vascular component.

Exceptional variations are referred to as glomangiomatosis and are characterised by a pattern of microscopically infiltrative growth and diffuse neoplastic growth [5,6]. The most common feature of a benign glomus tumour is a network of branching capillary-sized blood vessels that are layered with endothelial cells and encircled by collars of uniform glomus cells that form nests, sheets, and trabeculae and are mixed in with a stroma that is either hyalinized or myxoid. Glomus cells are characterised by a spherical shape, an amphophilic to eosinophilic cy-

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toplasmic border, and a rounded, sharply etched nucleus. The bland, homogeneous nuclear chromatin has discrete nuclei. Mitosis is a unique process. Glomus cells are layered within capillaries and the vasculature [5,6]. Three separate components of glomus cells, smooth muscle cells, and tiny vascular structures are articulated by the glomus tumour. The majority of the monomorphic, round to elliptical cells in the tumour mass have ovoid nuclei and eosinophilic cytoplasm. Cords, festooned sheets, and the arrangement of perivascular sleeves encircling the capillaries define cellular configurations [5, 6]. Significant nuclear atypia without mitotic activity or atypia-associated clinical features is the hallmark of a symplastic glomus tumour. The prognosis is still unchanged.

Significant nuclear atypia, aberrant mitotic figures, and mitotic activity are characteristics of malignant glomus tumours. A malignant glomus tumour may resemble a leiomyosarcoma or fibrosarcoma in terms of spindle cell histology. On the other hand, a benign glomus tumor's periphery is associated with sheets of malignant-looking round cells [4, 6]. A single, unusual microscopic characteristic in addition to nuclear pleomorphism is present in a glomus tumour with uncertain malignant potential, but the enunciation of the malignant criterion is not satisfactory. Atypical microscopic characteristics consist of deep-seated tumours larger than ≥2 cm and more than >5 mitosis/50 high power fields of mitotic activity. Oncocytic metaplasia can also be seen in its microscopic forms. Based on an ultrastructural analysis, a thicker basal lamina that surrounds each glomus cell and excludes the cellular junction is observed. Myofibrils and pinocytotic vesicles are representative of dense, intracytoplasmic structures (Fig. 1-10) [4,6].

Immune Histochemical Elucidation

The smooth muscle actin (SMA), muscle specific actin (MSA), CD34, calponin, h-caldesmon, and collagen type IV elicit strong immunological responses from globus tumours, while cytokeratin and S100 protein do not elicit strong immune responses. The vascular component is highlighted by CD34 immune staining. Ki-67 proliferation index is typically less than <5% and is visible in about 2% of neoplasms[6, 7]. The globus tumour exhibits a broad immune response to vimentin (100%), smooth muscle actin (99%), muscle-specific actin (95%), h-caldesmon (87%), and calponin 80%, while the immune response to CD34 is usually localised (32–53%). Type IV collagen and 91% of pericellular laminin are reactive to the immune system [6, 7]. The cytokeratin, CD31, S100 protein, CD68, CD57, Human Melanoma Black antigen 45 (HMB-45), CD117, desmin, chromogranin, synaptophysin, CD20, CD45, and Wilms' tumour gene 1 (WT1)

are all immune non-reactive to glomerus tumours.According to molecular research, more than 50% of benign and malignant glomus tumours exhibit chromosomal fusion of the MIR143-NOTCH gene. This genomic fusion can be assessed by Fluorescent In Situ Hybridization (FISH) [6].

Differential Diagnosis

The glomerus tumour necessitates separation from the related pericytic neoplasia and myopericytoma, which are derived from perivascular cells. Particularly in foci with prominent spindle cell differentiation, the cellular spectrum of the aforementioned neoplasia is identical to the histological and immune histochemical parameters of glomus tumours. Immune reactivity to keratin, immune non-reactivity to Smooth Muscle Antigen (SMA), and variable foci of epithelial or sebaceous differentiation are present in benign adnexal neoplasia, such as nodular hidradenoma or eccrine spiradenoma [7, 8]. The growth pattern of paragangliomas is characterised by notable zellballen configurations, which are made up of immune-reactive synaptophysin and chromogranin as well as sustantecular cells that are reactive to the S100 protein. Immune reactivity to keratin, synaptophysin, and chromogranin, as well as immune non-reactivity to Smooth Muscle Actin (SMA), are all present in neuroendocrine tumours. Nests of melanocytic cells that exhibit pigmentation, lack of accompanying vasculature, immunological reactivity to S100 protein, different melanocytic biomarkers, and immune non-reactivity to Smooth Muscle Antigen (SMA) and h-caldesmon are the constituents of dermal nevus [7,8]. Angio-leiomyoma is made up of smooth muscle fascicles, lacks a noticeable round cell component, and exhibits a desmin-induced classical immunological response [7].

Investigative Assay

Magnetic Resonance Imaging (MRI) is a useful tool for localising glomus tumours to determine their extent before choosing the best surgical course of action. A well-defined mass can be seen on T1 weighted images, which appear dark, and on T2 or T1 post gadolinium fat saturation, which shows a bright, contrast-enhancing image [6, 8]. When using Magnetic Resonance (MR) angiography, there is a significant enhancement in the arterial phase and a relevant tumour blush that becomes more pronounced, particularly in the delayed phase. An opaque, hypoechoic mass with potential bone erosion is seen on ultrasonography. Attenuation of the overlying cortical bone can be seen on radiographic examination, especially in subungual tumours [6, 7].

Prognostic Outcomes

A benign glomus tumour shows little recurrence after partial surgical removal. Unusual clinical characteristics are associated with unfavourable prognostic results. The aforementioned tumours are classified as glomus tumours of uncertain malignant potential, and they can exhibit features like a deep-seated tumour, a size of approximately >2 cm, or the occurrence of unusual mitotic figures. Moreover, a poorer prognosis is linked to necrosis, mitotic figures greater than >5 per 50 high power fields, or the co-occurrence of increased nuclear grade and mitotic activity [4,5].

Therapeutic Options

A benign glomus tumour can usually be treated effectively with just observation. A thorough surgical excision is an appropriate treatment for a benign glomus tumour, and it also helps to relieve pain, reduce neurological symptoms, and stop the tumour from relapsing. To create a surgical bed free of bleeding that is appropriate for total tumour eradication and inhibits recurrence, surgical removal is best carried out under loupe magnification or with a tourniquet [7, 8]. Given that the location of the lesion determines the surgical approach, tumour incrimination of the neighbouring bone can be sufficiently excised or curetted. For a central, subungual glomus tumour, the adjacent nail must be removed at the same time. A surgical result that is both aesthetically pleasing and functionally appropriate with a satisfactory level of pain resolution is considered acceptable [7, 8]. The trans-ungual approach for direct surgical excision is a typical procedure, but it is linked to a nail deformity. On the other hand, a lateral sub-periosteal approach increases the likelihood of recurrence but decreases the possibility of nail deformity [7, 8]. A carefully thought-out, initial surgical procedure is appropriate to reduce the tumefaction. To increase the proportion of cure, lesions that are not susceptible to shelling can be treated with deep-seated and peripheral curettage [7, 8]. Distal bony phalanx can frequently be flattened by periungual glomus tumours, which also stick to the periosteum.

Careful curettage of the implicated bone can prevent the tumour from returning. 10% of tumour relapses are thought to result from insufficient surgical removal of the tumour. Anti-inflammatory medication administration is inadequate. Thorough surgical excision of the tumour is effective, although it depends on the size and location of the tumour. It is beneficial to evaluate the tissue of a glomus tumour of unknown significance prior to surgery. To preserve spinal stability, tumours involving the lateral spine may be treated with unilateral fixation and fusion using pedicle screws [7, 8]. It is arguable whether unilateral or bilateral surgical screws are preferable for proper lumbar fixation because both approaches have similar risks and benefits in terms of therapy and surgical complications. However, unilateral lumbar fixation has a shorter recovery period and causes less hemorrhage[7, 8]. The majority of cases are followed by a complete curettage or the reduction of clinical symptoms once tumefaction is removed. Low back pain can be caused by spinal tumours of small size or infiltration, which can be treated by coherent radiofrequency ablation, a surgery that has a better prognosis than other options [7, 8]. When it comes to malignant tumours, en bloc surgical resection is an option. An enlarged glomus tumour may be difficult to remove. A big tumour in the lumbar or abdominal cavities requires complete removal along with spinal canal decompression, albeit there may be severe bleeding during surgery [8]. Both doxorubicin and olaratumab, which are effective in treating relapsing neoplasia and metastatic illness, are suitable treatments for malignant glomus tumours. Further research is necessary before administering immune checkpoint inhibitors or NOTCH pathway inhibitors to treat glomus tumours [8].

Conclusion

The smooth muscle actin (SMA), muscle specific actin (MSA), CD34, calponin, h-caldesmon, and collagen type IV elicit strong immunological responses from globus tumours, while cytokeratin and S100 protein do not elicit strong immune responses. The glomus tumour needs to be separated from angioleiomyoma, dermal nevus, nodular hidradenoma, eccrine spiradenoma, and myopericytoma. The diagnosis of the tumour can be made using plain X-rays, magnetic resonance imaging (MRI), and magnetic resonance angiography (MR). A poor prognosis is linked to characteristics like deep-seated tumefaction, magnitude of approximately >2 cm, atypical mitotic figures, necrosis, mitotic figures greater than >5 per 50 high power fields, or concomitance of enhanced nuclear grade with mitotic activity. A thorough surgical excision can be an appropriate treatment for a benign glomus tumour, which is amenable to simple observation.

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