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The Spheroid Smarting- Glomus Tumour

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Received Date: 18-04-2020; **Accepted Date:** 29-04-2020; **Published Date:** 07-05-2020

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Abstract

Glomus tumour is benign, perivascular hamartoma arising from glomus apparatus or a mesenchymal neoplasm essentially comprised of modified smooth muscle cells, also termed as glomangioma, glomangiomyoma or glomangiomas. Glomus tumour can arise from bi-allelic inactivation of Neurofibromatosis type 1 (NF1) and emerges in concurrence with NF1 gene. Also, decimation of neurofibromin within glomus cells activates the RAS-MAPK pathway. A gradually progressive, faintly tinged, bluish-red, subungual papule demonstrating a classic triad of symptoms as localized sensitivity, pain upon exposure to cold and intense pain with minor trauma is exhibited. Morphologically, a combination of glomus cells, smooth muscle cells and cogent vascular elements is discerned. Spheroid, punched out nuclei surrounded by minimal cytoplasm, an amphophilic to eosinophilic stroma and circumscribing branching, capillary sized vasculature is delineated.

Keywords

Glomus Tumour; Lesions; Spinal Canal; Tumefaction

Introduction

Glomus tumour is an exceptional, benign, perivascular hamartoma arising from glomus apparatus. Glomus tumour is generally beneath <1 cm magnitude and is morphologically

Bajaj A | Volume 1; Issue 1 (2020) | JCIM-1(1)-03 | Review Article

Citation: Bajaj A. The Spheroid Smarting- Glomus Tumour. J Clin Immunol Microbiol. 2020; 1(1):1-13.

DOI: <http://dx.doi.org/10.46889/JCIM.2020.1103>

comprised of glomus bodies. Glomus bodies are commonly situated within the arterioles, anastomotic blood vessels and efferent veins. Glomus tumour emerges from modified glomus cells which are specialized smooth muscle cells functioning as chemoreceptors. Normally, glomus cells regulate vascular outflow within the capillaries on account of environmental and inherent temperature alterations [1]. Glomus tumour is cogitated as a mesenchymal neoplasm essentially comprised of modified smooth muscle cells arising from the glomus body. Peripheral glomus tumours are consistently benign and enunciate severe pain, tenderness, evolve gradually and miniature tumours are difficult to discern wherein tumour detection can be delayed. The exceptional malignant glomus tumour is enlarged, exceeding 2 cm in magnitude, profound and visceral. Giant, intravenous glomus tumour can also ensue. Malignant glomus tumours can also be termed as glomagiosarcoma [1,2]. Pertinent to specific morphology, glomus tumour can be additionally nomenclated as glomangioma, glomangiomyoma or glomangiomas. However, site specific misnomers such as glomus faciale, glomus jugulare, glomus tympanicum or glomus vagale are essentially indicative of paragangliomas. Glomangiopericytoma is a terminology employed for glomus tumour displaying a prominent, hemangiopericytic vasculature. Nevertheless, aforesaid tumours are diverse from pericytic neoplasm or sinonasal glomangiopericytoma discerned at specific sites [1,2].

Disease Characteristics

Glomus tumour is a benign neoplasm with an exceptional, malignant variant. Glomus tumour displays an estimated proportion of 1.6% and is usually beneath <2% of soft tissue neoplasms. Glomus tumour predominantly arises in adults betwixt 20 years to 40 years, peaks within third to fifth decade and depicts an equivalent gender predisposition. Nevertheless, subungual lesion demonstrates a female preponderance with a female to male proportion of 3:1. Incrimination of spinal canal is extremely exceptional and glomus tumour can engender cogent neurological symptoms with compromised spinal cord and nerve roots. Glomus tumour is frequently delineated as miniature lesions situated upon distal extremities such as the hand, especially subungual region demonstrating a concentration of glomus bodies. Additionally, glomus tumour can occur in diverse sites such as the lung, stomach, pancreas, liver, gastrointestinal tract or genitourinary tract [2,3]. Malignant glomus tumour is associated with definitive morphological features such as deep-seated tumefaction, atypical mitotic figures and tumour magnitude exceeding >2 cm wherein enlarged neoplasia are situated at sites such as paravertebral region or thoracic cavity. Tumefaction can be benign or atypical with accompanying vertebral disruption, tumour extension into adjacent spinal canal via an expanded intervertebral foramen and consequent, intermittent back pain. Severe clinical symptoms arise on account of continual tumour evolution. Spinal cord compression is exemplified on Magnetic Resonance Imaging (MRI) [3,4].

Disease Pathogenesis

Glomus tumour with concurrent expression of Neurofibromatosis type 1 (NF1) gene usually arises from bi-allelic inactivation of NF1. Also, decimation of neurofibromin within glomus cells activates the RAS-MAPK pathway. Familial glomus tumour, demonstrating glomovenous malformation, is engendered by inactivating mutations within glomulin gene which are commonly expressed within vascular smooth muscle cells [3,4]. Specific instances can display concurrent genomic translocation with consequent oncogenic activation of NOTCH pathway, essentially induced by translocation within MIR143 promoter region. Glomus tumour commonly arises from Sucquet-Hoyer canal of glomus body which is primarily a specialized arteriovenous, anastomotic formation regulating heat within cutaneous surfaces and is denominated by a layered circumscription of epithelioid glomus cells, immune reactive to Smooth Muscle Antigen (SMA). Cold temperature ensures a relaxation of glomus cells along with patent vascular anastomosis which redirects vascular outflow within cogent capillary networks in order to conserve body heat and regulate temperature [2,4].

Clinical Elucidation

Tumefaction is gradually progressive and exhibits a faintly tinged, bluish-red, subungual papule accompanied with a classic triad of symptoms such as localized sensitivity, pain upon exposure to cold and intense pain with minor trauma. With pertinent clinical symptoms, glomus tumour can be adequately discerned with Magnetic Resonance Imaging (MRI). Glomus tumour is a predominantly cutaneous lesion frequently encountered upon subungual region of the finger although no site is exempt. Although glomus tumour can comprehensively emerge within various locations, frequently incriminated sites are the upper extremity (62%) and fingers (27%) wherein subungual lesions are common. Adjunctive sites delineating glomus tumour are trunk wall (11%), internal locales (11%), lower extremity (9%) or head and neck (7%). Atypical and malignant variants of glomus tumour are frequently deep-seated, in contrast to benign tumours [4,5]. Glomus tumour displays symptoms such as paroxysms of extraneously radiating pain disproportionate to magnitude of the neoplasm. Pain can also be elicited with altered temperature or tactile stimulation and is accompanied by hypoesthesia, muscle atrophy or osteoporosis. Certain glomus tumours arising within fingers and toes are associated with enunciation of NF1 gene. Incriminated bony structures demonstrate erosion and lytic lesions. Deep-seated glomus tumours are challenging to discern and can be misinterpreted as neurilemmoma or paraganglioma when subjected to imaging studies [4,5].

Histological Elucidation

The solitary neoplasm denominates a well-defined, bulging, un-encapsulated, darkly tinged, reddish tissue with a component of miniature nerve fibres. Superficial lesions are generally beneath <1.0 cm magnitude. Cut surface demonstrates an irregular, nodular and haemorrhagic tumefaction. On fine needle aspiration, cohesive clusters and aggregates of uniform, round cells with scanty cytoplasm are intermingled with scattered, amorphous, magenta coloured ground substance, foci of haemorrhage and occasional inflammatory cells [4,5]. Glomus tumour demonstrates a morphological combination of glomus cells, smooth muscle cells and cogent vascular elements. The cellular component exhibits spheroid, punched out nuclei surrounded by an amphophilic to eosinophilic stroma along with a circumscription of branching, capillary sized vasculature. Diverse, spheroidal cells with individual, regular, round to ovoid nuclei devoid of significant nuclear pleomorphism are exemplified [4,5]. Malignant metamorphoses of glomus tumour is characterized by a) significant nuclear atypia and associated mitotic activity or b) atypical mitotic figures in concurrence with metastasis, encountered in up to 40% instances. On microscopic examination, a well circumscribed nodule is encountered, principally composed of glomus cells, smooth muscle cells and cogent vasculature. Majority (75%) of instances are constituted by a solid variant wherein glomus tumour is predominantly comprised of glomus cells, inadequate vasculature and infrequent smooth muscle cells [5,6]. Glomangioma is a neoplasm discerned in an estimated 20% instances and demonstrates a predominant vascular component. Glomangiomyoma is enunciated in an estimated 5% subjects and is denominated as a tumour with prominent vascular and smooth muscle cell component. Exceptional variants are designated as glomangiomas and are described by a diffuse neoplastic growth and microscopically infiltrative pattern [5,6]. Benign glomus tumour preponderantly exhibits a branching network of capillary sized blood vessels, layered with endothelial cells, circumscribed by collars of uniform, glomus cells configuring nests, sheets and trabeculae, intermingled in a hyalinised or myxoid stroma. Glomus cells exemplify a spheroidal outline, a rounded, sharply etched nucleus localized within an amphophilic to eosinophilic cytoplasm and an indistinct cytoplasmic border. Nuclear chromatin is bland, homogenous and displays inconspicuous nuclei. Mitosis is exceptional. Vasculature and capillaries are layered with glomus cells [5,6]. As glomus tumour enunciates three distinct components of glomus cells, smooth muscle cells and miniature vascular structures, the tumour mass is principally comprised of monomorphic, round to elliptical cells with eosinophilic cytoplasm and ovoid nuclei. Cellular configurations are articulated by cords, festooned sheets and arrangement of perivascular sleeves surrounding the capillaries [5,6]. Symplastic glomus tumour delineates significant nuclear atypia with a lack of mitotic activity or clinical features associated with atypia. The prognosis remains unaffected. Malignant glomus tumour is denominated by significant nuclear atypia, mitotic activity and atypical mitotic figures. Malignant glomus tumour can depict a spindle cell histology to recapitulate a leiomyosarcoma or fibrosarcoma. Alternatively, sheets of malignant appearing round cells are enunciated in association with a peripheral component of a benign glomus

tumour [4,6]. Glomus tumour of uncertain malignant potential demonstrates unsatisfactory enunciation of malignant criterion although a singular, atypical microscopic feature in addition to nuclear pleomorphism can be observed. Atypical microscopic features are constituted by deep-seated tumours with magnitude exceeding ≥ 2 cm and mitotic activity in excess of >5 mitosis/50 high power fields. Microscopic manifestations of oncocytic metaplasia can also be discerned. On ultrastructural examination, a thickened, basal lamina is cogitated which envelops individual glomus cells in exclusion of cellular junction. Pinocytotic vesicles and myofibrils are exemplified in association with dense, intracytoplasmic bodies (Fig. 1-10) [4,6].

Figure 1: Glomus tumour depicting numerous branching, vascular channels lined by rounded glomus cells and intermingled smooth muscle cells.

Figure 2: Glomus tumour with branching blood vessels intermixed with sheets and aggregates of round to oval glomus cells depicting scanty, indistinct cytoplasm and bland nuclei.

Figure 3: Glomus tumour with sheets and cords of spheroidal glomus cells with inconspicuous nuclei and indeterminate amphophilic cytoplasm along with foci of haemorrhage.

Figure 4: Glomus tumour with branching vasculature and an admixture of clustered glomus cells with rounded nuclei and smooth muscle cells.

Figure 5: Glomus tumour with aggregates of spheroidal glomus cells with indistinct cytoplasm and uniform nuclei along with a commingling of smooth muscle cells.

Figure 6: Glomus tumour delineating aggregates of round glomus cells with uniform nuclei and poorly defined cytoplasm intermixed with curvilinear blood vessels.

Figure 7: Glomus tumours showing aggregates and fascicles of spheroidal glomus cells intermixed with numerous branching blood vessels and smooth muscle cells.

Figure 8: Glomus tumour demonstrating several branching, staghorn blood vessels along with nests and clusters of spheroidal glomus cells with minimal cytoplasm and a distinct smooth muscle component.

Figure 9: Glomus tumour exhibiting benign clusters of glomus cells with spheroidal, uniform nuclei, intermixed with branching vasculature and smooth muscle component.

Figure 10: Glomus tumour with sheets and clusters of glomus cells with minimal cytoplasm, round nuclei along with elongated vascular elements and a specific smooth muscle component.

Immune Histochemical Elucidation

Glomus tumour is immune reactive to Smooth Muscle Actin (SMA), Muscle Specific Actin (MSA), CD34, calponin, h-caldesmon, collagen type IV and immune non-reactive to cytokeratin or S100 protein. CD34 immune staining highlights the vascular component. Ki-67 proliferation index is discernible in approximately 2% neoplasms and is usually beneath <5% [6,7]. Glomus tumour demonstrates a comprehensive immune reactivity to vimentin (100%), smooth muscle actin (99%), muscle specific actin (95%), h-caldesmon (87%), calponin 80% with a typically focal immune reaction to CD34 (32 to 53%). Collagen type IV and pericellular laminin (91%) are immune reactive [6,7]. Glomus tumour is immune non-reactive to 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). On molecular analysis, chromosomal fusion of MIR143-NOTCH gene is exemplified in exceeding >50% of benign and malignant glomus tumours, a genomic fusion which can be evaluated by Fluorescent In Situ Hybridization (FISH) [6].

Differential Diagnosis

Glomus tumour requires a segregation from a myopericytoma and associated pericytic neoplasia originating from perivascular cells. Cellular spectrum of aforesaid neoplasia is identical to histological and immune histochemical parameters of glomus tumour, especially in foci with prominent spindle cell differentiation. Benign adnexal neoplasia such as nodular hidradenoma or eccrine spiradenoma demonstrate varied foci of epithelial or sebaceous differentiation, immune reactivity to keratin and immune non reactivity to Smooth Muscle Antigen (SMA) [7,8]. Paraganglioma demonstrates a growth pattern with significant configurations of zellballen composed of sustentacular cells immune reactive to S100 protein along with immune reactive synaptophysin and chromogranin. Neuroendocrine tumour displays a typical "salt and pepper" nuclear chromatin, immune reactivity to keratin, synaptophysin and chromogranin and immune non reactivity to Smooth Muscle Actin (SMA). Dermal nevus is composed of nests of melanocytic cells demonstrating a presence or absence of pigmentation, absence of associated vasculature, immune reactivity to S100 protein, various melanocytic biomarkers and immune non reactivity to Smooth Muscle Antigen (SMA) and h-caldesmon [7,8]. Angio-leiomyoma is comprised of fascicles of smooth muscles, is devoid of prominent round cell component and depicts a classical immune reactivity to desmin [7].

Investigative Assay

Magnetic Resonance Imaging (MRI) is efficacious in localizing glomus tumour in order to delineate the extent prior to deciding an optimal surgical approach. MRI exemplifies a well-

defined mass which appears dark upon T1 weighted images and demonstrates a bright, contrast enhancing image on T2 or T1 post gadolinium fat saturation [6,8]. Magnetic Resonance (MR) angiography is associated with an intense enhancement within the arterial phase and a pertinent tumour blush which amplifies in magnitude, especially within the delayed phase. Ultrasonography demonstrates a solid, hypoechoic mass with a possible erosion of the underlying bone. Radiographic examination can exhibit an attenuation of overlying cortical bone, particularly within subungual tumours [6,7].

Prognostic Outcomes

Benign glomus tumour displays minimal reoccurrence upon incomplete surgical excision. Atypical clinical features are concordant with adverse prognostic outcomes and aforesaid neoplasms are designated as glomus tumour of uncertain malignant potential which delineate manifestations such as a deep-seated tumefaction, magnitude of around >2 cm or occurrence of atypical mitotic figures. Additionally, necrosis, mitotic figures exceeding >5 per 50 high power fields or concurrence of enhanced nuclear grade with mitotic activity is associated with an inferior prognosis [4,5].

Therapeutic Options

Generally benign glomus tumour can be appropriately managed with simple observation. Benign glomus tumour is adequately treated with a comprehensive surgical extermination which is also beneficial in alleviating neurological symptoms, relieving pain and preventing tumour relapse. Surgical removal is preferably performed with a tourniquet or loupe magnification in order to create a haemorrhage-free surgical bed which is suitable for complete tumour extermination and prevents reoccurrence [7,8]. Tumour incrimination of the adjacent bone can be adequately excised or curetted as approach to surgery is contingent to location of lesion. Centric, subungual glomus tumour requires a concurrent eradication of abutting nail. An acceptable surgical outcome is defined as a functionally appropriate and aesthetically pleasing effect with satisfactory resolution of pain [7,8]. Direct surgical excision via a trans-ungual route is a standardized manoeuvre, although associated with a nail deformity. In contrast, a lateral sub-periosteal approach reduces possible nail deformity although reoccurrence is proportionately enhanced [7,8]. A scrupulously planned, preliminary surgery is suitable for alleviating the tumefaction. Lesions unamenable to shelling can be subjected to peripheral and deep-seated curettage in order to augment percentage of cure [7,8]. Periungual glomus tumour can commonly flatten distal bony phalanx and adhere to periosteum. Meticulous curettage of incriminated bone can circumvent tumour reoccurrence. An estimated 10% of tumour relapse arises on account of inadequate surgical extermination. Administration of anti-inflammatory drugs is unsatisfactory. Comprehensive surgical resection of the

tumefaction is efficacious and contingent to magnitude and location of neoplasm. Preoperative tissue evaluation of glomus tumour of indeterminate significance is advantageous. Tumours incriminating lateral spine can be managed with unilateral fixation and fusion with employment of pedicle screws in order to maintain spinal stability [7,8]. Adoption of unilateral versus bilateral surgical screws for appropriate lumbar fixation is debatable as aforesaid manoeuvres are associated with identical therapeutic outcomes and surgical complications. Nevertheless, unilateral lumbar fixation requires a reduced operative time and is minimally haemorrhagic [7,8]. Majority of instances are accompanied by decimation of clinical symptoms following removal of tumefaction or a comprehensive curettage. As incrimination of sacral and lumbar spine initiates a low back pain, spinal tumours of minimal magnitude or infiltration can be managed with cogent radiofrequency ablation, a procedure which is accompanied by superior prognosis [7,8]. En bloc surgical resection is applicable to malignant tumours. Resection of enlarged glomus tumour can be complicated. Enlarged tumour within the abdominal cavity or lumbar region mandates a comprehensive extermination with accompanying spinal canal decompression, although significant intraoperative haemorrhage can ensue [8]. Malignant glomus tumour can be suitably treated with doxorubicin and olaratumab, agents which are efficacious in managing relapsing neoplasia or metastatic disease. Administration of NOTCH pathway inhibitors or immune checkpoint inhibitors for treating glomus tumours require additional evaluation [8].

Conclusion

Glomus tumour is immune reactive to Smooth Muscle Actin (SMA), Muscle Specific Actin (MSA), CD34, calponin, h-caldesmon, collagen type IV and immune non-reactive to cytokeratin or S100 protein. Glomus tumour requires a segregation from a myopericytoma, paraganglioma, nodular hidradenoma or eccrine spiradenoma, dermal nevus or angioleiomyoma. Magnetic Resonance Imaging (MRI), Magnetic Resonance (MR) angiography and plain X-ray is pertinent in diagnosing the neoplasm. Features such as a deep-seated tumefaction, magnitude of around >2 cm, atypical mitotic figures, necrosis, mitotic figures exceeding >5 per 50 high power fields or concurrence of enhanced nuclear grade with mitotic activity are associated with an inferior prognosis. Benign glomus tumour is amenable to simple observation and can be adequately treated with a comprehensive surgical extermination.

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