

Unusual Glomus Tumor of the Penis

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Key Words

Glomus tumor • Subungual region • Hamartomas • Penis • Pain

Abstract

Introduction: Glomus tumors are benign neoplasms commonly found in subungual regions of the extremities and rarely located in the penis. Misdiagnosis of glomus tumors is common; therefore, symptoms and clinical presentations should be reviewed. **Objective:** The primary objective of this review article is to emphasize the pathogenesis, pathology, clinical presentation, symptoms, diagnosis, and treatment methods of glomus tumors in order to better identify and manage the condition. **Materials and Methods:** Research was conducted using PubMed/Medline. The inclusion criteria required glomus tumor to be present on the penis. **Results:** Glomus tumors, which appear as symptomatic or asymptomatic lesions, are attributed to dispersion grouping of neoplastic or non-neoplastic lesions in a particular area. **Conclusion:** Differential diagnosis of glomus tumors includes hemangiomas, neurofibromatosis, epithelial lesions, and spindle-cell lesions. Physical examination and histological findings should be used for diagnosis. Treatment options can be either conservative or invasive, in which the patient undergoes surgical excision.

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Introduction

Glomus tumors are rare neoplasms found mostly in subungual regions of the extremities. They are frequently benign soft tissue tumors that arise from the glomus body, a component of the dermis layer involved in thermoregulation and skin circulation [1]. Certain red or blue nodules are usually benign and sometimes asymptomatic. However, there are rare malignant lesions that are usually misdiagnosed as hemangiomas or venous malformations [2, 3]. Symptoms include paroxysmal pain by temperature change or pressure. Histologic staining methods are diagnostic of glomus tumors. Surgical removal of the glomus tumor, with postoperative follow-up to avoid recurrence or malignancy, is essential.

Historical Perspectives

Glomus tumors have been described in almost every part of the body. Hippocrates recorded cases of glomus tumors during the ancient Greek era [4]. The first accurate clinical description was by William Wood who described the tumors as “painful subcutaneous tubercles” in 1812 [4]. In 1878, Kolaczek described the subungual location of the glomus tumor, but classified it as variant angiosarcoma [4]. In 1924, Paul Masson published descriptions of the first histological features of glomus tumors [5, 6].

Pathogenesis and Pathology

Glomus tumors are mesenchymal neoplasms that comprise up to 2% of soft tissue tumors [6, 7]. The majority of glomus tumors are found on fingers or toes [8]. Glomus tumor is caused by a large number of neoplastic or non-neoplastic lesions either dispersed or grouped in an anatomical area. The glomus body is a thermoregulator in the form of arteriovenous anastomosis localized in dermal and precoccygeal soft tissue [9–11]. Glomus tumors are composed of varying proportions of vessels, smooth cells, and glomus cells. The common subungual tumors are well-circumscribed proliferations of capillary-sized vessels surrounded by cuffs of glomus cells. Glomus tumor is associated with neurofibromatosis, which is a common disorder that arises secondary to mutations in the tumor suppressor gene NF1 [9].

Brems et al. [9] discussed an association between germ line, somatic mutations, and glomus tumors. Germ line mutations in NF1 were found in all subjects presenting with glomus tumors. Somatic NF1 mutations were identified in alpha-SMA-positive glomus cells and were associated with NF1 glomus tumors.

Unusual features of atypical glomus tumors include large size, deep location, infiltrative growth, mitotic activity, nuclear pleomorphism, and necrosis [12]. Atypical features are usually observed in the center with a rim of benign appearing glomus tumors. Malignant glomus tumors frequently feature a deep location, a diameter of more than 2 cm, infiltrative growth, atypical mitotic figures, moderate to high nuclear grade, and 5 mitotic figures or more [13–16].

Glomus tumors often occur in children and adolescents, with prevalence towards males. Multiple glomus tumors are more prevalent in females. Most glomus tumors are solitary, but about 10% exist as multiple variants with hereditary familial tendency [17–20]. The gene for the multiple inherited variant has been linked to chromosome 1p21–22.3. This mutation is transmitted in an autosomal dominant fashion with incomplete penetrance and occurs 10% of the time. Expression of these inherited tumors vary by individuals [21].

Glomus tumors may be asymptomatic or symptomatic with local pain. Glomus tumors arise as small blue-red nodules from the glomus body, which is found in the adventitial layer of the blood vessels. A normal glomus body is an arteriovenous shunt related to thermoregulation [9, 22]. Glomus tumors are benign hamartomas that arise in areas rich with glomus bodies, located in the subungual regions. The mass is a neuro-myoarterial receptor

that normally acts as a thermal regulator and regulates arteriolar blood flow of skin temperature [7]. The normal glomus body is comprised of both smooth muscle cells and epithelial-type cells surrounded by a fibrous capsule [22]. Glomus tumors in the penis are rarely found in the distal region of the glans penis.

Glomus tumors of the penis and soft tissue tumors are rare. There are very few cases reported in the literature. Glomus tumors occur on the glans penis, on the right corpora of the penis, and as periurethral masses [7, 9, 21, 23–26]. Penile lesions are sometimes accompanied by glomus tumors in the fingers and feet [22]. Clinical presentations of glomus tumors of the penis may be asymptomatic or have symptoms such as tenderness to palpitation, priapism, and perineal pain [21–23]. Cells from the glomus tumor of the glans penis were arranged in cords, and demonstrated no pleomorphism or increased mitotic activity [7].

Pathologists should recognize morphological variations of glomus tumors. Misdiagnosis of the glomus tumors as neurofibromatosis frequently occurs [5, 9]. Harrison et al. [27, 28] used Fisher's statistical test to identify and assess the significance of the association between these two conditions. They discovered that 29% of the patients with glomus tumors also had a history of neurofibromatosis, providing a strong epidemiologic association [27, 28]. Epithelioid glomus tumors are also of particular importance because they may be mistaken for epithelial lesions of spindle-cell lesions, such as schwannoma, leiomyoma, hemangiopericytoma. Immunohistochemical and ultrastructural studies indicate that epithelioid glomus tumors have characteristics identical to those of conventional glomus tumors. The cells showed features consistent with smooth muscle derivation. The epithelioid areas frequently exhibited cytological atypical features that were believed to be manifestations of cellular degeneration rather than evidence of neoplastic progression [29].

High power field high nuclear grade alone, infiltrative growth, and vascular space involvement are not associated with metastasis. A symplastic tumor is an atypical glomus tumor that reveals high-grade nuclear pleomorphism without large size, deep location, infiltrative growth, mitotic activity, and necrosis. Despite its high-grade nuclear pleomorphism, its behavior is benign [30]. Glomangiomas are a rare presentation of glomus tumor described as glomus cells in an angiomas [31]. It reveals histologic features of diffuse angiomas and excess glomus cells [12].

Genetic Aspect of Glomus Tumors

Mosquera et al. [32] study indicated that a fusion of MIR143-NOTCH fusions were prominent in benign and malignant tumors.

Location of Glomus Tumors

Glomus bodies are naturally distributed around the body in the skin, specifically in subungual regions [24]. Glomus tumors in the subungual or subcutaneous region are usually solitary, but multiple lesions have been found on the glans penis [21]. Glomus tumor develops as small blue-red nodules usually located in the deep dermis or subcutis of upper or lower extremities [6]. Tumors arise from growth of one or more components of the normal glomus body. Tumors are not restricted to typical regions. They appear in areas without normal glomus bodies. Glomus tumors can also be found as “glomangioma”—a benign vascular tumor typically encountered at extremities, but also rarely in stomach, lung, urethra, or vagina [29]. Rare encounters of glomus tumors can also present on the glans penis [7, 21, 22, 25, 33].

Symptoms and Clinical Presentation of Glomus Tumors

Subcutaneous nodules may vary from red, purple, or blue, depending on the depth of the lesions. Glomus tumors of the penis often present as localized masses with pain. Male pediatric patients present with penile lesions of dilated vascular spaces filled with blood, surrounded by rims of glomus cells [7]. The tumor may also emerge with localized tenderness and sensitivity to colder temperatures and palpitation. If these tumors are stimulated by cold, they precipitate a temperature change of the entire extremity.

Glomus tumors of the penis can be asymptomatic for many years through adolescence. Although patients with benign glomus tumors often find it painful, patients with malignant masses typically complain of discomfort. Malignant glomus tumor of the penis can develop as priapism and mild phimosis [7, 23]. In rare instances, multiple congenital glomus tumors may present as painless, plaque-like lesions [23].

Soft glomus tumors on the shaft of the penis have a 66.7% chance of being malignant. A case study patient, who presented with a malignant tumor of the penis,

had an initial symptom of priapism, but it was caused by post-traumatic vascular injury leading to an arterio-lacunar fistula [23]. Another young male adult patient with painful lesions on the glans penis exhibited mild phimosis [7].

Additional cases reported by Kamarshv et al. [34] and Enzinger et al. [35] also showed benign tumors located in the subungual of the index finger in 62 and 78 year old females, which were defined as a glomus tumor exhibiting nuclear atypia similar to malignant tumors. From these findings, cellular atypia and nuclear pleomorphism are not considered a definite marker of malignancy [34].

Malignant glomus tumors found in soft tissues can metastasize to cardiac and pulmonary areas [3, 23, 36]. The former lesions in patients have led to metastases and recurrence after the excision of the tumor [13–16, 37]. A case study by Folpe et al. [37] documented 7 recurrences, 8 metastases, and 7 deaths from the disease.

Clinical Diagnosis of Glomus Tumor of the Penis

A triad of excruciating pain, localized tenderness, and cold sensitivity is the key to diagnosing the glomus tumors [2]. Hildreth's test, known as the “ischemia test”, helps diagnose glomus tumors by asking patients to palpate and assess the tenderness of the site of pain [38]. This test involves decreasing and increasing blood flow via inflation and deflation of a cuff surrounding the tumor. Hildreth's test is positive if pain decreases on inflation and increases on deflation [39]. Other diagnostic steps include transillumination of digits, pinpoint localization, ice test, and spraying of alcohol to freeze the area and produce pain [3, 36–39]. Love's test locates the pain and tenderness to a specific site by using a pinhead, ball-point pen, end of a paperclip, or Kirschner wire to press on the skin covering the tumor [37, 40, 41].

The mechanism of pain generation in patients with glomus tumor is related to exposure to cold temperature. The activation of transient receptor potential (TRP) channels is responsible for pain. TRP channels are cellular sensors that generate temperature and pain sensations, and are stimulated by physical and chemical changes in the tumor bed [42–44]. Transient receptor potential melastatin (TRPM)-8 is a temperature sensitive ion channel with a threshold of about 26–31°C [45]. It is activated by cooling and noxious cold [46]. TRPM-8 is found in sensory neurons that transmit nociceptive neural signals to the spinal cord and brain. TRP channels are involved

in local dilation and constriction of blood vessels and can evoke pain, thus explaining the correlation between temperature sensitivity, vasodilation, and pain in glomus tumors [44].

Histology Including Electron Microscopic Findings of the Glomus Tumor

Diagnosis of glomus tumors of the penis is based on MRI, microscopic, and immunohistochemical findings [21, 23]. However, treatment of glomus tumors should not be solely based on clinical findings as some tumors that histologically test positive for malignancy may behave as benign masses [26].

Histologically, glomus tumors show positive reactions of the tumor cells to smooth muscle alpha, smooth muscle actin and vimentin [22, 23]. There are endothelium-lined vascular spaces surrounded by masses of epitheloid cells, which were divided as vascular, myxoid, and solid masses [2, 47, 48]. The tumor cells exhibit a polygonal, uniform appearance of round to ovoid nuclei, with single large nucleoli with a slightly eosinophilic cytoplasm, forming solid sheets of cells interrupted by vessels of varying size [2]. Vessels surrounding glomus tumors contain thick cellular walls and small lumen that make up the Suquet-Hoyer canal [49]. The vessels of the tumor increase in number, consisting largely of glomus cells. Nonmyelinated nerves lie along the border of the cell wall in close proximity to nearby Schwann cells and fibroblasts. Basal lamina surrounds individual cells of the cell wall and fibrils fill the cytoplasm [49]. The glomus tumors show differentiation toward smooth muscle tissue, so detection of actin isoforms is a positive confirmation of glomus tumors [50].

Under electron microscope, the tumor cells prove to be smooth-muscle cells; therefore, the glomus tumor is a tumor-like lesion of mesodermal origin rather than a true neoplasm [2, 20, 47].

Routine stains of glomeri reticulin impregnation are done in addition to hematoxylin and eosin staining for the cells presented in the male patient. The glomus cells of the penis reveal a positive cytoplasmic immunopositivity for the pan-muscle positive and negative for desmin, CD31, and CD34 [21]. Histological examination of the periurethral tumor show positive for vimentin, desmin, and calponin and negative for desmin, factor VIII-related antigen, S-100 protein, neurofilament, cytokeratin, and epithelial membrane antigen [2, 24, 29, 42, 43]. Other smooth muscle markers, including smooth muscle actin,

muscle-actin, caldesmon, and smooth muscle myosin are negative [24]. Additional findings reveal smooth muscle features of tumor cells, such as pinocytotic vesicles, external laminae, dense plaques, and thin filaments with dense bodies scattered within the cytoplasm [2, 42, 43]. Few cell junctions and focal basement membrane-like structures are observed. Most benign lesions are small, often between 0.1 and 0.3 cm in diameter and less than 1 cm.

Malignant tumors stain positive for smooth-muscle actin [23]. Biopsies and histological examinations reveal tumors from multiple patients that are greater than 2 cm in diameter in visceral locations, which reveals nuclear atypia, increased nucleo-cytoplasmic ratio, and an increase in mitotic activity [3, 23, 34, 36]. Additionally, malignant glomus tumors exhibiting glomangiomas feature diffuse angiomas and excess glomus cells [37]. On the other hand, metastatic tumors did not result from tumors that showed high nuclear grade in the absence of any other malignant features, high mitotic activity and superficial location only, large size only, or deep location only [37].

Radiology of Glomus Tumors

Radiological diagnosis of glomus tumors includes ultrasound, angiogram, MRI, cavernosography, and duplex Doppler to reveal vascularity. Histological findings are favored over radiological findings in the diagnosis of glomus tumors; however, MRI and arteriography are used to observe tumor regression after treatment administration [51, 52].

Treatment of Glomus Tumors

Glomus tumors are removed surgically to give patients complete relief from pain and sometimes from concomitant circumcision [23, 35]. Two surgical approaches are transungual and periungual [2]. Following general anesthesia and tourniquet control, glomus tumors are surgically removed [3, 36]. Post-operative follow-ups are essential to exclude extragenital lesions after surgery [7, 21]. Benign glomus tumors of the penis need radical surgery to avoid local recurrence [29]. Circumcision can be used to treat penile glomus tumors with phimosis. Surrounding tissue that appears normal is removed with the tumor to exclude malignancy [21, 25, 29, 53].

Malignant tumors are treated with a combination of embolization and chemotherapy. MRI and arteriography can be performed to monitor the regression of the pe-

nile tumor [23]. Macaluso et al. [7] described a case in which a malignant mass was removed by performing a cavertonomy. Depending on the severity and nature of the tumor, chemotherapy, resection, or other surgical procedures may be required [22, 23].

Furthermore, a rare case such as non-ischemic high-flow priapism was treated using an oral alpha-adrenergic and diagnosed by MRI. The patient suffered from syncope and dyspnea two weeks after embolization and later received chemotherapy after glomangiosarcoma was found. The penile tumor was excised because of persistent erectile dysfunction and perineal pain [23].

Conclusion

The occurrence of glomus tumors in the penis is rare. Glomus tumors usually occur as benign neoplasms and infrequently become malignant. Most are solitary, but 10% occur as multiple lesions. Frozen sections of glomus tumors with appropriate stains are diagnostic. The tumors are surgically excised. Biopsies and specific stains are utilized to confirm the presence of glomus tumor. The postoperative recurrence rate of glomus tumors is approximately 10%. MRI and arteriography can often detect postoperative recurrence. It is pertinent that patients follow-up with their physicians regularly to avoid recurrence of cancer and metastases.

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