ORIGINAL ARTICLE

Eastern Journal of Medicine

East J Med 27(3): 357-363, 2022
DOI: 10.5505/ejm.2022.78466

Comparison of Digital and Extradigital Glomus Tumors

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ABSTRACT

Glomus tumors (GT) are the rare neoplasms of soft tissue originated from mesenchymal origin. GTs are formed from glomus cells, smooth muscle cells and arteriovenous structures. Although the GT can be seen in throughout the body, finger pulp and subungual location are seen in ¾ of cases. In this study, we aimed to compare the clinical, radiologic and histopathological features of finger localized GT (digital) and GTs located outside the fingers (extradigital). The effect of localization and surgical margin on the recurrence was compared.

The diagnosis of GT was searched from the database of Adana Seyhan State hospital between date of 2010-2020. Thirty-six patients with finger localized GT as group 1 and twenty patients with extra-digital GT as group 2 were included in the study. The groups were evaluated and compared with regards to the demographic characteristics, clinical findings, radiographic imaging, the preoperative diagnosis, operation time, tumor size, the number of lesions, the histopathological sub-types, the results of immunohistochemical analysis, the surgical margin status, clinical follow-up results and recurrences.

56 patients were diagnosed with GT during the 10-years study period of hospital database search. The mean age of patients was 42 (±17), the mean follow-up time was 44 months (±24). The number of patients with pulp, subungal and distal finger localized GT was 36 (group1) and the number of patients with extradigital tumor was 20 (Group 2). When all the lesions examined, the most frequent lesion was found nevus (28.6%), GT (26.8%) and haemangioma (17.9%). The number of tumoral foci was single in 51 patients (91.1%) and twice in 5 (8.9%) patients. The mean tumoral size was measured as 6 mm (±4.2). The results of αSMA, MSA, vimentin and calponin positivity in immunohistochemical analysis were found to be similar between groups.

The finger localized tumors are diagnosed correctly with higher percentage clinically. The extradigital GT reaches higher size and usually misdiagnosed. There are more recurrences in patients with positive tumor cells at the surgical margin after operative treatment. The immunohistochemical staining for differentiating the malignant tumors seems non-beneficial. It is thought that giving attention to have negative surgical margin in digital GTs prevent the recurrences.

Keywords: Digital, Extradigital, Glomus tumor, Immunohistochemistry

Introduction

Glomus tumors(GT) are the rare neoplasms of soft tissue originated from mesenchymal origin.(1) It is usually benign and comparise the s1.6 % of all of tissue tumors. (2) The Glomus Word which means sphere was firstly used by Wood at 1812. The glomus body which is the source of glomus tumors is responsible for thermo-regulation via neuromyoarterial receptors located between arteriol and venules at subcutaneous tissue(3). Masson made the histopathologic definition of the tumor at 1924.(2) GTs are formed from glomus cells, smooth muscle cells and arteriovenous structures. (4) Alpha-Smooth Muscle Actine (αSMA), Muscle Specific Actine (MSA) and h-Caldesmon are characteristically detected in histopathological examination of GT, beside these it shows non spesific vimentine and type 4 collagen expression (5,6). Although the GT can be seen in throughout the body, finger pulp and subungual location are seen in ¾ of cases. (7). The digital and subungal localization are frequently seen in women, whereas the extradigital GTs in men. The tests used in the diagnosis are Hildreth, Love pin and cold sensitivity evaluations. (8) The triad of sharp pain, point precision and excessive sensitivity to cold is the classical sign. They are generally lower than the size of centimetres. Despite their small size, the symptoms appear to be severe. It can be confused with neurinoma, dermatofibroma and hemangiomas in clinical diagnosis.(9) It is recommended to think the GT diagnosis in patients with symptoms and evaluation with magnetic resonance imaging and ultrasound to detect its localization.(10) The gold standard method for curative treatment in GTs which have very rare potential of malignant transformation

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Received: 07.10.2021, **Accepted:** 07.02.2022

is the excision with negative surgical margin. In our study, we aimed to compare the clinical, radiologic and histopathological features of finger localized GT(digital) and GTs located outside the fingers (extradigital). The effect of localization and surgical margin on the recurrence was compared.

Material and Method

The diagnosis of GT was searched from the database of State hospital between date of 2010-2020. The GT diagnosis was written in the records of 66 patients. Eight patients were excluded due to the inconclusive diagnosis of GT and 2 patients excluded due to the diagnosis of gastric glomus tumor. The all glomus tumors located throughout body including cutaneous and subcutaneous tissue were included in the study. The patients were divided as thirty-six patients with finger localized GT as group 1 and twenty patients with extra-digital GT as group 2. The groups were evaluated and compared with regards to the demographic characteristics, clinical findings, radiographic imaging, the preoperative diagnosis, operation time, tumor size, the number of lesions, the histopathological sub-types, the results of immunohistochemical analysis, the surgical margin status, clinical follow-up results and recurrences. The evaluation of 23 cases which have missing parameters of immunohistochemical analysis were repeated. α-Smooth Muscle Actin (αSMA), Muscle Specific Actin (MSA), vimentin, calponin, CD34, CD31, cytokeratins and S100 positivity were evaluated and the groups were compared. The tumor size, atypic mitotic activity, high nuclear grade and increased mitosis were considered for the criteria of malignancy. The ethical board approval was taken from Adana City hospital with number of 68/1102 at 21.10.2020.

Statistical Analysis: SPSS (IBM SPSS for Windows ver.23) program was used for the statistical analysis of data. The categorical measurements were expressed as number and percentage. The continuous measurements were expressed as mean, standard deviation, minimum and maximum. Shapiro-Wilk test was used for detection of normally distribution of data. Chi-square test and Fischer's Exact test were used for comparisons of categorical variables. Independent T-test was used in groups with normally distributed and Mann Whitney-U test was used non-normally distributed groups. The statistical significance level was accepted as 0.05 in all tests.

Results

56 patients had diagnosis of GT in the search of hospital's database during the 10 years period. The mean age of patients was 42 (±17), the mean follow-up time was 44 months (±24). 34 patients were women and 22 patients were male. The number of patients with pulp, subungal and distal finger localized GT was 36 (group1) and the number of patients with extradigital tumor was 20 (Group 2). (Table 1)

The most common complaint was pain. Magnetic resonance was preferred for radiologic evaluation in Group 1 patients and ultrasound was preferred for Group 2. When all the lesions examined, the most frequent lesion was found nevus (28.6%), GT (26.8%) and hemangioma (17.9%). The number of tumoral foci was single in 51 patients (91.1%) and twice in 5 (8.9%) patients. The most common subtype was glomus tumor with solid structure 73.2% (41/56). Two patients (%3.6) had diagnosis of malignant glomus tumor. When the distance to the surgical margin evaluated, 2/56(%3.5) of patients had positive surgical margin. These patients were the ones who had diagnosis of benign glomus tumor. Two patients developed recurrence on follow-up examinations and underwent re-excision with large surgical margin. The complaints of 53/56(94.6%) of patients resolved after surgical excision. The mean tumoral size was measured as 6 mm (±4.2). The digital glomus tumor was more frequent in women however, there was no statistical difference (p=0.174).

The magnetic resonance was the predominant radiologic method in Group 1, whereas, ultrasound was in group 2. The preoperative diagnostic accuracy was 33% and 5% in Group 1 and Group 2, respectively. The tumoral involvement of multiple foci was similar between groups. The mean tumor diameter was 9.2 mm (±5.2) in Group 2 and 4.1mm (±1.5) in Group 1 and this was statistically significantly larger (p=0.001).

There were two patients with positive surgical margin in group 1. All patients in group 2 had clear surgical margin. The mean operation time was 23 min. in group 1 and was 13 min in group 2. There was no statistical difference with regards to the histological sub-types between groups (p=0.181). One patient in group 1 had continuation of complaint after surgical excision. The complatins of all patients in group 2 resolved completely. The data of groups are presented in Table 2.

Table 1. Demographic and Clinical Data

	n=56
Location site	
Digital(group 1)	36
Extradigital(group 2)	20
Recurrence	2/56
Admission symptom	
Pain	26 (46.4%)
Mass	10 (17.9%)
Colour changes	9 (16.1%)
Increased pain with temperature change	11 (19.6%)
Preliminary diagnosis	
Nevus	16 (28.6%)
Glomus tumor	15 (26.8%)
Haemangioma	10 (17.9%)
Lipoma	8 (14.3%)
Fibroma	7 (12.5%)
Histopathologic diagnosis	
Benign	54(96.4%)
Malign	2(3.6%)
Pathologic subgroup	
Solid type	41(73.2%)
Glomangioma	12(21.4%)
Glomanioma	3(5.4%)

The results of αSMA, MSA, vimentin and calponin positivity in immunohistochemical analysis were found to be similar between groups. Although there was no statistical significance, the CD34 positivity in group 2 was significantly higher (p=0.015). Cytokeratin, S100 ve CD31 staining was not found in any patients in both groups. There was no patient diagnosed with malignant GT in Group 1. Two patients diagnosed with malignant GT in Group 2. The follow-up time after surgical excision was 46 months and 40 months in group 1 and 2, respectively (p=0.680). The results of immunohistochemical analysis are presented in Table 2.

Discussion

The histopathology of glomus tumor was first defined by Barre and Masson at 1924. It was called as subcutaneous painful tubercules formerly. (11) The glomus tumors are typically formed by three components: glomus cells, smooth muscle cells and vascular structure. (4) GT is seen mostly at fingers due to its origin from glomus body. There are many sites reported other than the finger localization as internal organs like stomach, lung and colon. (12) Digital GT are frequently seen in middle aged women whereas, there is no gender difference in extradigital GTs. It is usually single but can be seen multiple. (13) Marco et al. reported in their study including 138 patients that it is diagnosed mostly in 4-6 decades. It is seen in women more frequently than men with 63.6%. The most common localization is hand finger (51 %). (4) Van et al reported that is distributed equal in all ages. (14) In our study, 60.7 % of all patients were women. The finger localization was 66.6 % in women and 50% in men. The digital GT rate in women was consistent with literature as higher but it was not statistically significant (p=0.170). There was no difference in terms of gender distribution (p=0.170) and age (p=0.240) between group 1 and 2. The diagnosis was made mostly at 3. and 4. decades in all patients. There was a higher in incidence of digital GT localization (64.3%) than the reported studies in the literature. Küçük et al. conducted a study that evaluate the role of MRI in digital GT diagnosis and reported that 76.2 % (61/80) of patients had subungual localization. (15) When we

Table 2. Comparison of Demographic, Clinical and Histopathological Characteristics of The Groups

	Group 1 n=36	Group 2 n=20	P
Gender			
Female/Male	24/12	10/10	0.170
Age	43(±18)	39(±15)	0.240
Radiologic imaging			
USG	7/36	7/20	0.000
MR	19/36	0/20	0.001
Number of multiple lesions	3/36	2/20	0.590
Tumor size (milimeter)	4.1(±1.5)	9.6(±5.2)	0.001
Malign/Benign	2/34	0/20	0.590
Operation duration (min)	23.8(±7)	13(±5.9)	0.002
Follow up time (month)	46(±23)	40(±26)	0.680
Recurrence	2/34	0/20	0.400
αSMA staining	36/36	20/20	0.877
MSA staining	35/36	20/20	0.640
Vimentin	34/36	20/20	0.400
Calponin	32/36	19/20	0.400
CD 34	8/36	11/20	0.010
CD 31	3/36	2/20	0.877

evaluated the finger localized tumors in our study, 13 patients out of 36 (36.1%) had pulpa localization.

The classical symptom of GTs is pain. The main presenting symptom of patients is pain. In the study by Van et al. including 51 patients with diagnosis of GT, all patients had sensitivity and 80% had pain. Pain, discoloration, and nail deformities increased by cold were less reported complaints. (14) The most common presenting symptom was pain in 26 patients (46.4%) in our study. 10 patients had diagnosed after painless lesion presentation and 9 patients had diagnosed after pain formed by cold presentation. The pain complaint was found lower in our study than reported in the literature.

The diagnosis of GT could be done after the application of diagnostic tests and evaluating the patient's complaint and remembering the GT diagnosis. The sensitivity of tests, features and accuracies are different. Tingmao et al. recommended in their study that the accuracy rate of tests can be increased by applying different tests together. (8) The most frequent diagnosis reported in GT differential diagnosis are hemangioma, leiomyoma, intradermal nevus, schwannoma and some vascular lesions. (13,16) The most frequent diagnosis was nevus in 18 (32.1%) in our study and 13 ones had GT. The other diagnosis was hemangioma, fibrom and lipoma with decreasing rates. The prediagnosis rates were not different wbetween the two groups (p=0.060). The accuracy of prediagnosis was statistically significantly higher in group 1. (p=0.010) The fact that extra-finger localization may be rarer was thought to be effective in this result. The fact that we do not encounter GT very often and the differences in symptoms were evaluated as the reason for our low accuracy of pre-diagnosis compared to the literature.

Imaging methods are frequently used to help the diagnosis and performed surgery. Various imaging methods are used. Although ultrasound provides detailed information about the location and size of the tumor, it may be insufficient to describe the specific features of the lesion. (17) Chen et al. reported that bone destruction can be seen up to 50% in patients, and that lesions of 2 millimeters and above can be diagnosed with 100% accuracy with

Doopler Ultrasound. (18) The sensitivity of MRI was reported to be 90% in the same study. In another study by Al-Qattan et al. reported that because of its low specificity, less than 20% negative predictive value, and high cost, MRI was recommended as a second-line examination after color doppler ultrasound. (19) Küçük et al. reported in their study that the false negative rate of MRI increased in small lesions. (15) There are also publications reporting that MRI is superior to other methods in the detection of recurrent and multiple tumors. (20) It has been noted that reports describing the features of MRI in extradigital GTs are less comprehensive.

(21). In our study, 19 (52.7%) of Group 1 patients were evaluated with MRI, while MRI imaging was not performed in any patient in Group 2. The rate of those evaluated by USG was 19.4% in Group 1 patients, while it was 65% in Group 2. While the preference for MRI was statistically significantly higher in the examination of Group 1 patients (p=0.001), USG evaluation was more preferred in Group 2 patients (p=0.001).

Although GT is usually small and solitary, it is rarely encountered in more than one-centimeter size and multiple ones in patients. It is reported that the tumor diameter usually greater than 1-3 cm in patients with multiple GT. (22) Marko et al, reported in their study that the median size of GT as 6 mm. The tumor size of digital GT was smaller than the extradigital GT. (4) In our study, 3 patients in group 1 and 2 patients in group 2 had multiple GT. The difference between groups was not statistically. (p=0.590) The size of these tumors was between 3 to 9 mm. The mean tumor size was 4.6 mm and 9.6 mm in Group 1 and 2, respectively. (p=0.001) It was thought that the diagnosis of GTs located in the fingers was made earlier, since they usually cause symptoms in smaller sizes.

The standard treatment method for glomus tumors is surgical excision. It should be noted that the surgical excision be done without any residual disease and creating any deformities. The excision of multiple lesion should be done under the supervision of imaging methods. Although deformity is not a very common complication in tumors located outside the finger, care should be taken in tumors located on the finger. It is reported in the literature that patients who don't accept the recommended treatment of surgical excision can be managed with sclerotherapy, argon or carbon dioxide laser (2). The nail plate can be removed and excision with enucleation can be achieved with minimal deformity in subungal GTs (8). Van et al. reported in their study that successful treatment can be applied after enucleation with the transungal approach (14). There are also studies suggesting a lateral surgical approach to prevent deformity (23,24). 23 cases in Group 1 were subungal localization in our study. All these patients were operated with transungal approach. The surrounding tissue of GT in Group 2 were tried to excised completely. The mean operation time was 23 min(sd±7) in Group 1 and 13 min(sd±5.9) in Group 2. The operation time in Group 1 was statistically significantly longer (p=0.002). It was thought that the small surgical area, the effort to reduce the deformity and the high blood supply caused this period to be prolonged.

The inadequate surgical excision of GT may cause recurrences. The reported rates of recurrences after GT surgery are low in the literature. The recurrence rate in two years follow-up period reported to be 2.2% by Marco et al., 3.3% by Van et al. and 5 % by Justin et al.(4,14,25) The patients with positive surgical margin have increased recurrence rate up to 30 % (26). It is recommended that in order to prevent recurrences, some studies recommend excision of the tumor beyond the visible margins (27). We could not find a study in the literature with an objective recommendation for the excision of surgical margin.
It is stated in many studies that the absence of GT cells at the surgical margin will be sufficient for treatment (4,14). It is not always possible to provide extensive surgery in finger localized tumors as it may cause deformities. It is easier to have large surgical margin in extradigital localized tumors. Another factor that leads to the development of recurrence is potential of malignity or presence of malign lesions (8). Second surgical interventions require more careful and complete surgical excision. In our study, two patients had recurrence. These cases had digital GTs. Tumor sizes of the relapsed cases were 5 and 7 millimeters. In both cases, subungal localization was present. There was no sign of malignancy in the patients who were reported to have GT at the surgical margin in the pathological examination. Recurrences developed two months and four months after the first surgical intervention. It was determined that the complaints of the patients did not improve after surgical excision.

The absence of recurrence in 54 patients without tumor at the surgical margin, regardless of their proximity to glomus tumor cells, suggested that the absence of tumor cells at the surgical margin might be sufficient. Dramatic improvement in symptoms after appropriate surgical excision in GTs is remarkable.

The most important complications are recurrences and nail bed deformities in finger localized GTs (28). Van et al reported 3.3% nail deformity after surgical excision (14). Tingmao et al. reported this rate as 4% (8). In our study, nail deformity developed in three

patients in Group 1 after surgical treatment. Two patients underwent re-excision due to the local recurrence. In the other patient, nail bed deformity and healing were observed after subungal placement. No complications were observed in the patients in Group 2. Deformity occured in 5.3% of patients when considering the all cases.

Glomus tumors are divided into 3 different subtypes in pathological examination. Solid GT (70%) is the most common variant, followed by glomangioma (25%) and glomangioma (5%). Vascular density and smooth muscle content are remarkable in the differentiation of subtypes (5). Although they are separated according to the differences in their ultrastructural characteristics, they have a benign structure and similar clinical features. In our study, it was observed that solid GT was 73%, glomangioma 21%, and glomanioma was 6% in subtyping. There was no statistical difference between the groups in the distribution of subtypes (p=0.180). There was no statistically signigicant difference between the results of evaluation of tumor size and subtype (p=0.800).

Positive staining for CD34, α-SMA, neuron-specific enolase (NSE) and vimentin, and negative staining for cytokeratin and S100 is remarkable in the evaluation made by immune histochemical techniques In the pathological examination of glomus tumors (29). Almost similar features were observed in studies on the staining properties of malignant glomus tumors and benign glomus tumors (30). Marco et al reported in their study that the positive staining for αSMA as 99 %, vimentin as 100%, CD 34 as 32% and actin as 95 % in GTs. While S100 stained 2%, desmin and keratin did not show staining (4). In our study, the pathological examination of the patients whose immunohistochemical evaluation was incomplete was evaluated and all of them were evaluated. Positive staining for αSMA 100%, MSA 98%, Calponin 91%, CD34 33% and vimentin 96% were determined as a result of the evaluation. There was no staining in cytokeratin, S100 and CD 31 in any case. No significant difference was detected between the groups, except for CD34. It was determined that there was no difference between benign GT and malignant GT in terms of immunohistochemical staining.

It is known that malignant transformation is approximately 1% in glomus tumors (31). Folpe et al. published a study in 2021 and reported malignant features of GT in their study. They defined the malignancy criteria as being deeply located, larger than two centimeters, having more than five mitoses at 50 high magnification in microscopic examination, and nuclear atypia (6, 32). Although different subtypes of malignant GTs were defined in subsequent studies, similarities in their clinical behaviors are remarkable. The number of reported cases of metastases in malignant GTs is limited (33). There is no recommended surgical treatment other than wide excision in these patients. Close clinical follow-up is recommended after surgery due to the risk of recurrence and distant metastasis (29,34). Two patients had diagnosis of malignant GT in our study. It was remarkable that the rate of diagnosis of malignancy was 3.5% among all patients, which was higher than that reported in the literature. Both patients diagnosed with malignant GT were in Group 2. Tumor dimensions were measured as 21 millimeters and 24 millimeters. There was no recurrence or distant metastasis in the follow-up of the patients who underwent wide surgical excision.

Glomus tumors are rare benign lesions. Finger localized tumors are clinically correctly diagnosed at a higher rate. GT, which is located outside the finger, reaches larger dimensions and is often misdiagnosed. Frequent recurrences develop in patients with tumor cells at the resection margin in surgical treatment. Immunohistochemical staining does not appear to be useful in differentiating malignant tumors. It was thought that paying attention to excisions with tumor-free surgical margins in finger localized GTs would prevent recurrences.

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