Original Article

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Pathology Section

Giant Cell Tumour of the Tendon Sheath: Analysis of 35 Cases and their Ki-67 Proliferation Indexes

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ABSTRACT

Introduction: A giant cell Tumour of the tendon sheath (GCTTS) is a slow-growing benign Tumour originating from the synovial cells of the tendon sheath. It is the second most common Tumour of the hand. The aim of this study was to perform a retrospective clinicopathological evaluation of GCTTS cases and determine whether the proliferative activity of giant cell tumour of tendon sheath is related to its recurrence rate and local aggressiveness.

Materials and Methods: The age, gender, Tumour location and diameter, treatment mode, Ki-67 proliferation index, mitotic rate, and recurrence were retrospectively evaluated in 35 patients diagnosed with GCTTS in the Department of Pathology, School of Medicine, Recep Tayyip Erdogan University between 2009 and 2014.

Results: Of the 35 GCTTS cases, 23 were female, and 12 were male. The mean age was 45 y (range 10–70). Sixteen Tumours were located in the right hand and 14 in the left hand, and five were in the feet. The mean Tumour diameter was 2.3 cm (0.6–6 cm). All patients underwent marginal excision. The mean postoperative follow-up period was 4 y (range 28 months–5 y). Only six patients showed recurrence. In these cases, the site of GCTTS recurrence was the phalanx of the hand. The mean Ki-67 index in the recurrence cases was 6.5%, whereas it was 2.3% in those without recurrence.

Conclusion: The Ki-67 proliferation index and mitotic activity were increased in recurrent cases compared to nonrecurrent cases. Therefore, these parameters may be helpful in predicting recurrence of GCTTS. However, adequate surgical excision and complete removal of the Tumour are important steps to minimize the recurrence rate.

Keywords: Giant cell tumour, Ki-67, Proliferation index, Recurrence, Tendon sheath

INTRODUCTION

A giant cell tumour of the tendon sheath (GCTTS) originates from the synovial cells of the tendon sheath. It has a slow clinical course and is one of the most common soft tissue tumours of the hand. Although less common, it may also be observed in the ankle, elbow, knee, wrist, spine, and fingers. The pathological nature of this disease is controversial. Some authors consider that it has a neoplastic nature, whereas other believe it is a non-neoplastic tumour. The underlying etiology is believed to include trauma, inflammation, metabolic diseases, and neoplasia. The most widely accepted pathogenic hypothesis is reactive or regenerative hyperplasia associated with an inflammatory process. The treatment of GCTTS is surgical excision. There is a high rate of recurrence of the tumour after excision. Many factors are considered as causing recurrence, including incomplete excision of the lesion, proximity to the distal interphalangeal joints, presence of degenerative joint disease, radiological erosion and increased mitotic activity. To prevent recurrence is complete surgical excision with removal of all satellite nodules if present [1-3]. We aimed to investigate the relation between GCTTS recurrence and the Ki-67 proliferation index. At the same time, we reviewed the literature and performed a retrospective analysis of clinicopathological findings of GCTTS.

METHODS

In this retrospective study, we evaluated 35 patients diagnosed with GCTTS in the Department of Pathology, School of Medicine, Recep Tayyip Erdogan University between 2009 and 2014. The parameters evaluated were age, gender, tumour location, treatment mode, and recurrence. Data from the clinic and pathology records were used. Sections 3-4 μthick were obtained from the paraffin embedded blocks belonging to the selected suitable preparations fixed with formalin to study a monoclonal mouse antibody to human Ki-67 immunohistochemical method on positively charged slide. An immunohistochemical study was carried out using the streptavidin-biotin method and Ki-67 primary antibody (MM1, Cod: 801704, prediluted). Aminoethyl carbazole was used as a chromogen. Reverse staining was performed with Mayer's hematoxylin, and the slides were cover slipped with mounting medium. The sections were examined under light microscopy.

For Ki-67 staining, proliferative index (PI) was expressed as a percentage of positively stained cells out of 1000 tumour cells counted in the most mitotically active areas. Only the nuclei with a significant stain were deemed positive for staining. The mitotic rate was counted on 10 randomly selected microscopic areas (×400).

Statistical analysis

Statistical assessments have been performed by using SPSS software (SPSS version 16; SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean±SD and medium (minimum-maximum). In comparison of these 2 groups, Mann-Whitney U test and T student test was used. The relationship between the variables was evaluated by Spearman's correlation analysis. Comparison of categorical variables was executed with Chi-square test. $p<0.05$ value was accepted to be statistically significant.

RESULTS

Of the 35 GCTTS cases surgically excised, 23 (66%) were female, and 12 (34%) were male. The mean age was 45 y (10–70). With regard to the location of the tumour, the GCTTS was in the right hand in 16 (46%) cases, the left hand in 14 (40%) cases, and the feet in 5 (14%) cases. The smallest tumour had a diameter of 0.6 cm, and the diameter of the largest was 6 cm. The mean tumour diameter was 2.3 cm. The most common tumour location was the first finger of the right hand. [Table/Fig-1] shows data on the tumour location, patient age and gender, mitotic rate, presence of recurrence, and Ki-67 proliferation index. Each patient underwent marginal excision. Six cases showed recurrence nearly two years after the operation. The patients presented due to a slow-growing

Patient No	Age	Sex	Tumor diameter	Localization	Recurrence	Mitotic rate (10 hpf)	Ki-67 index
1	58	F	1.7 cm	Right hand 2.phalanx volar surface	No	2	5%
2	32	F	4 cm	Right hand 2.phalanx volar surface	No	3	3%
3	70	M	2.2 cm	Left hand 1.phalanx volar surface	No	2	3%
4	54	F	1.8 cm	Right hand 5.phalanx volar surface	No	1	2%
5	54	F	2 cm	Left hand 1.phalanx dorsal surface	Yes	6	5%
6	49	F	5 cm	Right hand 3.phalanx dorsal surface	Yes	7	6%
7	44	F	1.5 cm	Right hand 2.phalanx volar surface	No	2	4%
8	33	M	1.6 cm	Left hand 1.phalanx volar surface	No	1	4%
9	64	F	2.2 cm	Right hand 2.phalanx volar surface	No	3	4%
10	51	M	2.5 cm	Left foot volar surface	No	3	3%
11	53	M	0.6 cm	Left hand 2.phalanx volar surface	Yes	5	6%
12	10	F	4 cm	Left wrist dorsal surface	No	2	5%
13	29	M	1.6 cm	Left hand 1.phalanx volar surface	No	3	2%
14	68	F	0.7 cm	Right hand 1.phalanx volar surface	No	3	4%
15	32	F	5 cm	Left foot dorsal surface	No	2	2%
16	25	F	2.5 cm	Right hand 4.phalanx volar surface	Yes	7	8%
17	31	F	2 cm	Left hand 1.phalanx volar surface	No	1	2%
18	38	M	4 cm	Left wrist dorsal surface	No	2	5%
19	25	F	1 cm	Right hand 5.phalanx volar surface	No	3	3%
20	52	M	1.4 cm	Left hand 2.phalanx volar surface	No	1	1%
21	49	M	1 cm	Right hand 1.phalanx volar surface	No	1	4%
22	25	F	1.5 cm	Left hand 3.phalanx volar surface	Yes	8	7%
23	59	F	1 cm	Right hand 3.phalanx volar surface	No	2	3%
24	47	F	1.5 cm	Left hand dorsal surface	No	2	1%
25	61	M	1 cm	Right hand 3.phalanx volar surface	No	3	4%
26	32	F	6 cm	Right ankle posterior surface	No	1	2%
27	35	F	2.5 cm	Left hand 1.phalanx volar surface	No	3	4%
28	54	F	2.5 cm	Right foot dorsal surface	No	2	1%
29	54	M	1.2 cm	Right hand 1.phalanx volar surface	Yes	9	7%
30	37	F	6 cm	Right foot volar surface	No	2	4%
31	42	F	0.6 cm	Left hand 5.phalanx volar surface	No	2	1%
32	57	F	1 cm	Right hand 5.phalanx volar surface	No	3	4%
33	64	F	2.8 cm	Right hand 3.phalanx volar surface	No	1	2%
34	50	F	2 cm	Right hand 4.phalanx volar surface	No	2	4%
35	36	M	2.1 cm	Left hand 2.phalanx volar surface	No	2	3%

[Table/Fig-1]: Clinicopathologic findings of Tumours

painless mass. We used X-ray, ultrasonography (USG), and magnetic resonance imaging (MRI) modalities. Conventional radiographic studies revealed grey shades within the soft tissue of some tumours. Two patients where the tumour was located in the foot had cortical bone destruction due to pressure of the mass [Table/Fig-2&3]. All the patients had firm and painless soft tissue masses, with well-defined borders. Most of the tumours had a subcutaneous location. The macroscopic examination revealed firm, lobulated, and nodular masses with cut surfaces of yellow-brown colour. The microscopic examination showed diffuse hyalinization areas, osteoclast-like multinuclear giant cells, stromal cells, xanthomatous histiocytes, and hemosiderin accumulation [Table/Fig-4].

The Ki-67 proliferation index differed in each tumour, as shown in [Table/Fig-1]. The mean Ki-67 proliferation index was 3.5% and varied between 1 and 8%. The mean Ki-67 index in recurrence cases was 6.5%, whereas it was 2.3% in those without recurrence. In one recurrent case, the initial Ki-67 proliferation index was 1%, but it had increased to 5% 2 y after recurrence. In the other recurrence cases, the index varied from 5% to 8%. The Ki-67 proliferation index increased in all recurrent cases [Table/Fig-5]. It was low in all nonrecurrent cases [Table/Fig-6]. The mitotic activity was increased in recurrent cases, with a mean of 7/10/hpf [Table/Fig-7]. Non recurrent cases had low mitotic activity, with a mean of 2/10 hpf. No atypical mitosis was observed in any of the cases.

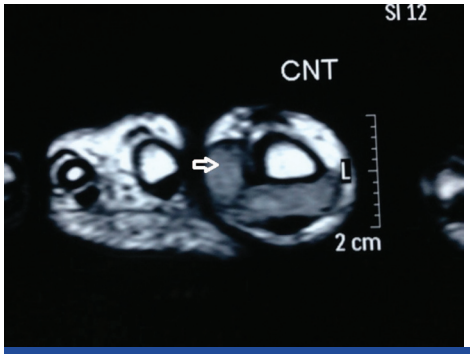
The Ki-67 staining percentage was different between the non-recurrence and recurrence groups ($p<0.001$), which is statistically significant (assessed by T-student test). The mitotic activity was different between the non-recurrence and recurrence groups ($p<0.001$), which is statistically significant (assessed by Mann-Whitney U-test). Statistically significant correlation has been found between Ki-67 staining percentage and mitotic activity ($p<0.001$) (Spearman's correlation test, r: 0.658).

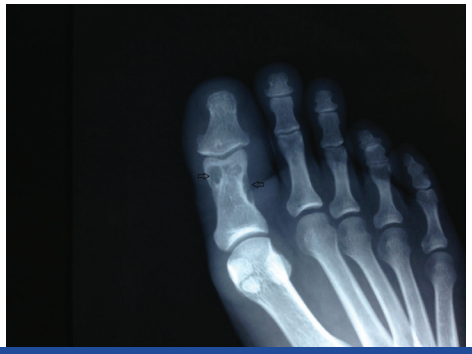
DISCUSSION

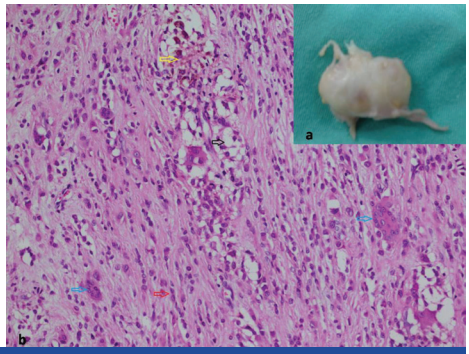
GCTTS was first defined as a fibrous xanthoma by Chassaignac in 1952 [4]. In the following years, it was referred to as a fibrous histiocytoma of synovium, pigmented nodular tenosynovitis, tenosynovial giant cell Tumour, localized nodular tenosynovitis, benign synovioma, and fibrous xanthoma of synovium [1,2,4-6]. The majority of these definitions are based on pathological findings. The most common location of GCTTS is the hand where it is observed on the palmar surface of the fingers. GCTTS is occasionally seen in other anatomic locations. It is the second most common soft tissue mass of the hand after ganglion cysts [4]. It presents as a slow-growing clinical Tumour and is generally observed in patients aged 30–50. The female-to-male ratio is 3:2 [1,5]. The female to male ratio (2:1) and ages of the patients in the present study are in accordance with those reported in the literature. GCTTS is classified into two types: diffuse and localized. The localized type is more commonly observed. The diffuse type, which is rare, is called pigmented villonodular synovitis. It is larger than the localized type, may be localized within the joint, and may lead to a limited joint range of motion. The localized type is often encountered in the hand, whereas the diffuse type is generally seen in the joints [1,3]. All our cases were nodular tenosynovitis of the localized type. We observed no diffuse type.

The recurrence rate after excision of GCTTS is 9–14% [3,6-8]. However, some studies reported a recurrence rate above 45%[1-3,8]. In the present study, the recurrence rate was 17% (n=6).Risk factors associated with the high recurrence rate include incomplete excision of the lesion, proximity to the arthritic joint, proximity to the distal interphalangeal joints of the finger and radiological erosion [1,3-5]. However, inadequate tumour excision is the most common factor associated with a high recurrence rate [1,2]. Lowyck and De Smet [9] determined a significant relationship between recurrence, pressure erosion, and degenerative joint disease. However, they found no significant correlation between recurrence and localization in the distal interphalangeal joint. Al-Qattan [10] noted that pressure erosion on the bone caused by the tumour should not be regarded as intraosseous invasion and proposed that a high recurrence rate is not related to pressure erosion. Moreover, Al-Qattan recommended a new classification to determine recurrence after surgical excision. The proposed classification contains two subgroups, Type I and Type II. Type I includes a single oval or multilobulated tumour, and Type II is defined as the presence of two or more tumours independent of each other. The distinction between Type I and II tumours is important in predicting the risk of recurrence. It is imperative to use surgical magnifying glasses during surgery to ensure that all satellite lesions are excised.

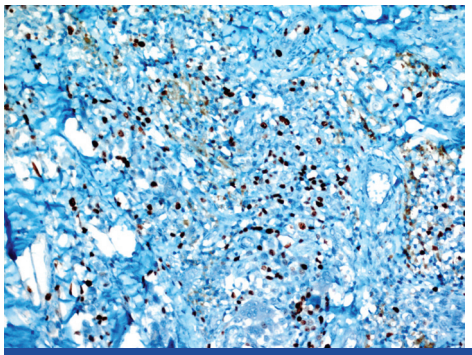
Some studies reported a relationship between the GCTTS location and tumour recurrence. In a study of 213 cases, Williams et al., [11] investigated the correlation between recurrence and localization in the hand in 27 recurrences. They reported that the risk of recurrence was higher in cases where the tumour was localized in the extensor tendons compared to localization in the flexor tendons and joint capsule. Darwish and Haddad [12] studied 52 cases involving 12

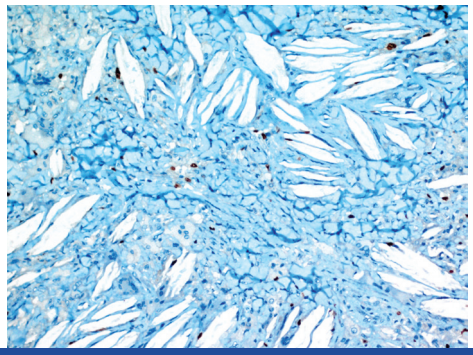


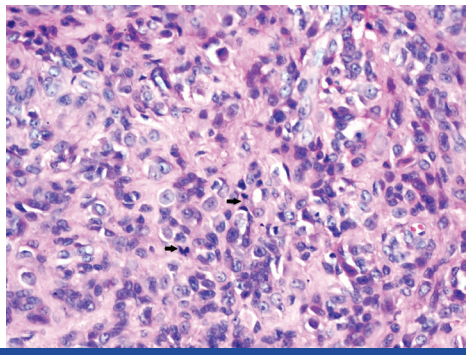




[Table/Fig-2]: Axial T2-weighted MRI image showing a hypointense mass lesion over the inferior and lateral aspects of the first manual phalanx (white arrow)., **[Table/Fig-3]:** Anteroposterior X-ray showing a bone destruction due to compression of the Tumour mass over the inferior and lateral aspects of the first pedal phalanx (black arrow). **[Table/Fig-4]:** a) Macroscopic appearance is Tumour nodules surrounded by a common pseudocapsule. ; b) Microscopic appearance is mononuclear cells (red arrow) among osteoclast-like giant cells (blue arrow), xanthomatous cells (black arrow), and haemosiderin pigment (yellow arrow) (H&Ex200)







[Table/Fig-5]: Ki-67 proliferation index high of the Tumour (Ki-67x200) **[Table/Fig-6]:** Ki-67 proliferation index low of the Tumour (Ki-67x200) **[Table/Fig-7]:** Tumour are increased mitotic activity (H&Ex400)

recurrences. They reported recurrence rate 24% (n:12). Reilly et al., [6] found that many tumour recurrences after excision were localized in the interphalangeal joint of the thumb and in the digital distal interphalangeal joint. The close relation between the borders of the tumours and the surrounding neurovascular structures and soft tissues contributes to adequate excision. The tendons and neurovascular structures in the flexor surface of the fingers are in a longitudinal position. The extensor tendon and associated anatomic structures, which provide expanded and constitute a natural covered, increase the risk that remnant tumour tissue will be left during the excision of tumours in the flexor surface hand compared to the extensor surface hand. In the present study, the tumours were located in the phalanx of the hand in the six recurrence cases.

GCTTS generally appears as a painless mass in the flexor surface of the hand and wrist Limited joint range of motion and sensory loss over the distal region are uncommon symptoms. The time required for formation of the tumour varies from just a few wk to 30 y [1,5]. Therefore, exact recurrence rates can be determined only by long-term follow-up.

Many theories for the pathogenesis of GCTTS, such as trauma, lipid metabolism disorders, osteoclastic proliferation, infection, vascular disorders, immune mechanisms, inflammation, neoplasia, and metabolic disorders, have been proposed [1,13]. Jaffe's theory [14] which suggests that GCTTS is the result of reactive or regenerative hyperplasia accompanied by an inflammatory process, is the most widely accepted.

In GCTTS cases, X-ray examination usually reveals a soft tissue mass, signs of bone pressure, and cortical erosion secondary to long-term pressure. USG is more popular in the diagnosis of soft tissue tumours of the extremities because it can more clearly display bone erosion secondary to close contact with the tendon sheath, as well as the vascularization, location, size, and echogenicity of the tumour. MRI is recommended for preoperative diagnosis. The characteristic findings of MRI include low signal intensity, T1- and T2-weighted images with similar or slightly higher signal intensity as compared to the skeletal muscle, and homogenous increases in gadolinium-enhanced T1-weighted images [1,2,5].

GCTTS presents as a yellow, firm, lobulated, nontender, nodular mass, which is macroscopically visible [1]. Although, nodular tumours can be excised without leaving any remnant in the surgical area, it is difficult to excise diffuse tumours, which have an infiltrative character. Ikede et al., [15] reported that small tumour remnants may be left in the excision area even in cases of nodular tumours. They suggested that microscopic excision was necessary in such cases. Moreover, they noted a relationship between diffuse tumours and the presence of bone erosion due to pressure.

GCTTS histopathology presents with hyperplasia in synovial cells, histiocyte accumulation, osteoclast-like multinuclear giant cells, hemosiderin-containing macrophages, and hyalinization, which is characterized by varying degrees of fibrous tissue growth [1]. Localized GCTTS has a capsule around the tumour, whereas diffuse GCTTS has a tendon sheath instead of a capsule over large areas [1,14,16]. Some studies reported no relation of recurrence with cellularity and high mitotic activity [3,11]. In contrast, Rao and Vigorita [7] found no initial relationship between mitotic activity and recurrence but observed high mitotic activity in all tumour cases with recurrence after twenty-seven months. Monaghan et al., [16] stated that high mitotic activity might not be a marker of recurrence and noted that the best method of preventing recurrence is complete excision of the tumour. Kitagawa et al., [17] used the MIB 1 staining index to investigate the potential relation of proliferative activity with local aggression and recurrence in 30 localized GCTTS cases. They found no link between proliferative activity, the recurrence rate, and local aggression in localized GCTTS. In the present study, the Ki-67 proliferation index and mitotic activity were increased in recurrent cases compared to non-recurrent cases.

Complete resection is very important to reduce the risk of recurrence in GCTTS. However, inadequate excision may occur when the Tumour has spread to adjacent synovial tissues [5,11,12,18]. Ozalp et al., [2] recommended using surgical magnifying glasses during

surgery to prevent inadequate excision. may be beneficial. Fotiadis et al., [19] reported ıntrinsic biology of the tumour shown play a more important role in recurrence than tumour location or local invasiveness. Kotwall et al., [20] reported that 48 patients included in the study, 14 received radiotherapy after surgery. They have been founded recurrence occurring only two (4%) patients. Jones et al., [21] also reported that postoperative radiotherapy was beneficial in patients with recurrence after marginal excision. However, the mechanism by which postoperative radiotherapy reduces tumour recurrence has yet to be revealed. Good results have been reported in cases treated with wide excision [6,19]. We applied no radiotherapy and only performed re-excision in the six recurrence cases.

CONCLUSION

Ki-67 and the mitotic rate may be helpful in the prediction of recurrence by determining the clinical course of GCTTS. Following marginal excision, recurrence is common in tumours located in the hand. To obtain an acceptable outcome in marginal excision of tumours and thus prevent any possible recurrence, complete excision of the tumours, with the aid of a surgical magnifying glass, should be performed.

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