Optimal Treatment for Tenosynovial Giant Cell Tumor of the Hand

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This review examines the following aspects of tenosynovial giant cell tumors (TSGCTs): the use of multiple names, the complex relationship between tumor growth pattern and location, the high rate of postoperative recurrence, local invasiveness, use of nonsurgical therapy with molecularly targeted drugs, and best current treatments. This tumor has been referred to by various names, but is now most frequently referred to as TSGCT. TSGCT is classified as localized and diffuse, in accordance with its growth characteristics. Most TSGCTs of the fingers are localized. TSGCT is likely a neoplastic process arising from synovial lining cells, in which tumor cells express the colony stimulating factor 1 (CSF1) gene. The postoperative recurrence rate of TSGCT is approximately 15%. The intrinsic characteristics of recurrence are not clear, and complete resection of the lesion is still the treatment mainstay. Moreover, TSGCT commonly grows out of a pseudocapsule. Therefore, to perform complete resection of TSGCT, surgery must be performed cautiously after appropriate preparation, by using anesthesia, a tourniquet, surgical loupe, and surgical microscopy. After accurate preoperative diagnosis, meticulous planning by surgeons is necessary. The lesion should be resected along with approximately 1-mm of healthy tissue at the adhesion site. In addition, because satellite lesions might be present near the tumor, careful dissection and observation of the color of surrounding tissue are important. International clinical trials of CSF1 receptor inhibitors for TSGCT treatment are ongoing. (J Nippon Med Sch 2020; 87: 184–190)

Key words: tenosynovial giant cell tumor, giant cell tumor of the tendon sheath, hand, finger, recurrence

Introduction

General orthopedic surgeons consider tenosynovial giant cell tumors (TSGCTs)—a common hand tumor—to be intractable because they have various problematic elements such as use of multiple names, a complex relationship between tumor growth pattern and location, high postoperative recurrence rates, and local invasiveness. In addition, molecularly targeted drugs are sometimes an effective treatment and must be considered by the surgeon. Therefore, this review discusses the characteristics of TSGCT and the best current treatments.

Nomenclature, Epidemiology, and Etiology

TSGCT is a benign lesion that originates from the synovia of the tendon sheath, joint, and bursa. It occurs most frequently in the fingers, followed by the ankles/feet, knees, wrists, and elbows. TSGCT is also known as giant cell tumor of the tendon sheath, localized nodular tenosynovitis, xanthoma, and pigmented villonodular synovitis (PVS) and was first described as tenosynovial giant cell tumor in the World Health Organization classification of 2013. TSGCT is classified as localized and diffuse, in accordance with its growth characteristics. Most localized tumors occur outside joints such as the tendon sheath of the hands, and most diffuse tumors occur within joints such as the knee. Most TSGCTs of the fingers are localized, occur in the tendon sheath, and essentially form a single nodular lesion. The frequency of TSGCT in the hand joints is 8% to 19%. TSGCT usually has a pseudocapsule with clear boundaries but may partially adhere to or invade surrounding tissue. Accordingly, in the assessment of surgical curability, TSGCT may be classified as wholly covered with a single pseudocapsule or as an incompletely covered tumor. In addi-
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FDS, flexor digitorum superficialis; FDP, flexor digitorum profundus.

Fig. 1 A tenosynovial giant cell tumor penetrating the flexor digitorum profundus tendon (arrow). FDS, flexor digitorum superficialis; FDP, flexor digitorum profundus.

docapsule. The skin of the fingers is connected to the phalanges by many ligaments, so it is less mobile, and there is a small gap where tumors cannot grow easily. Therefore, lesions tend to protrude into a space with less resistance and progress along the bone surface, thereby surrounding the phalanges. Furthermore, tumors grow out of the pseudocapsule. In fact, extracapsular lesions lose continuity with intracapsular lesions in approximately 30% of cases. About 5% of all TSGCT lesions are diffuse, with multiple granular-like lesions and no pseudocapsule, which is the counterpart of diffuse PVS.

TSGCT readily involves the tendon sheath and joint capsule, as well as the ligaments, tendons, palmar plate, and periosteum (Fig. 1). TSGCT also involves the skin in 2.3% of all cases. Bone changes are observed in 8% to 44% of cases. Most bone changes are pressure erosion; cystic bone disruption, commonly observed in PVS, is rare in TSGCT.

Recurrence

Surgery is the standard treatment for TSGCT. The recurrence rate is approximately 15%, which is high for a benign tumor. Table 1 shows reported postoperative recurrence rates. Mean time to recurrence is 2 to 4 years, although recurrent cases have been reported after more than 10 years. The clinical factors associated with TSGCT recurrence include the primary tumor at the interphalangeal joint of the thumb, as well as at the distal interphalangeal (DIP) joint of other fingers, presence of osteoarthritis near the tumor, presence of bone erosion, infiltration of the tendon and joint capsule, spread into the joints, neurovascular involvement, tumor spread outside the capsule, and piecemeal resection. All these factors present anatomical difficulties when performing complete tumor excision (Table 2).

The proliferative ability of cells may be an intrinsic characteristic associated with recurrence. On immunohistochemistry, the absence of the nm23 gene was associated with recurrence, but results from other studies were contradictory. Hence, the intrinsic characteristics of recurrent TSGCT are unclear, and complete resection remains the standard treatment.

Minimizing Recurrence Risk

Complete resection of TSGCT must be performed cautiously, with appropriate preparation and planning after accurate preoperative diagnosis.

1. Preoperative Diagnosis

The preoperative diagnosis rate of TSGCT is as low as...
Table 1  Postoperative recurrence rates of tenosynovial giant cell tumor

| Study                | Year | No. of cases | Recurrence rate (%) | Follow-up (months) |
|----------------------|------|--------------|---------------------|-------------------|
| Grover et al.        | 1998 | 52           | 15                  | 79 (7-174)        |
| Looi et al.          | 1999 | 53           | 7                   | (12-60)           |
| Reilly et al.        | 1999 | 70           | 27                  | 40 (7-138)        |
| Kotwal et al.        | 2000 | 48           | 4                   | 52 (24-132)       |
| Al-Qattan            | 2001 | 43           | 11                  | 48 (24-72)        |
| Kitagawa et al.      | 2004 | 30           | 13                  | 49 (12-126)       |
| Ikeda et al.         | 2007 | 18           | 6                   | 65 (12-192)       |
| Darwish et al.       | 2008 | 52           | 24                  | (36-120)          |
| Suresh et al.        | 2010 | 14           | 7                   | 51 (36-108)       |
| Williams et al.      | 2010 | 213          | 13                  | 51 (36-86)        |
| Garg et al.          | 2011 | 106          | 4                   | 144 (48-264)      |
| Jalgaonkar et al.    | 2011 | 47           | 9                   | 47 (25-124)       |
| Adams et al.         | 2012 | 50           | 10                  | (12-210)          |
| Di Grazia et al.     | 2013 | 64           | 5                   | (2-153)           |
| Lancigiu et al.      | 2013 | 96           | 8                   | 12 (5-29)         |
| Lautenbach et al.    | 2013 | 84           | 2                   | 56 (48-96)        |
| Bedir et al.         | 2014 | 35           | 17                  | 48 (28-60)        |
| Koutserimpas et al.  | 2018 | 36           | 11                  | 21 (2-58)         |
| Galbiati et al.      | 2019 | 27           | 11                  | (5-122)           |
| Linney et al.        | 2019 | 285          | 9                   | —                 |
| Ozben et al.         | 2019 | 50           | 6                   | 84 (38-173)       |
| Shi et al.           | 2019 | 135          | 10                  | 54 (24-103)       |

*aMean (range), bMean follow-up period not reported

Table 2  Risk factors identified in previous studies of postoperative recurrence of tenosynovial giant cell tumor

| Risk factors                                             | References |
|---------------------------------------------------------|------------|
| Occurrence at thumb interphalangeal joint or other     | #24        |
| distal interphalangeal joint                            |            |
| Presence of osteoarthritis near tumor                   | #24        |
| Presence of bone erosion                                | #19, 23, 24, 30 |
| Infiltration of tendon and joint capsule                | #4, 8, 18  |
| Tumor spread into joints                               | #8         |
| Neurovascular involvement                              | #32        |
| Tumor spread outside tumor capsule                      | #5, 6, 39  |
| Proliferative ability of cells                          | #34, 37    |
| Absence of nm23 on immunohistochemistry                | #23        |
| Multiple tumors                                         | #39        |
| Piecemeal resection                                     | #30        |

4%, and the highest rate was 42%. Preoperative diagnoses other than TSGCT include ganglion cyst, epidermoid cyst, foreign body granuloma, and sebaceous gland cyst, among others. Because these lesions are easier to resect, resection of TSGCT incorrectly diagnosed as one of these lesions might increase the risk of recurrence.

a. Plain radiography findings

TSGCT is the most common cause of bone erosion due to pressure caused by soft tissue tumors in the hands (Fig. 2), accounting for 67% of cases of soft tissue tumors. Other soft tissue tumors in the hands that cause bone pressure erosion due to pressure include glomus tumors, synovial chondromatosis, hemangiomas, lipomas, and schwannomas. In addition, malignant tumors, although rare in the hands, cause destructive bone changes.

b. Ultrasonography findings

Ultrasonography is useful for diagnosis of TSGCT. Typical ultrasonographic findings of TSGCT include a solid tumor with blood flow and occasional presence of...
satellite lesions. Differentiating between TSGCT and ruptured ganglion cyst is difficult.18,49.

c. Magnetic resonance imaging findings
Magnetic resonance imaging (MRI) is useful for diagnosis of TSGCT16,50, which typically shows isointense to slightly hyperintense signals, as compared with muscle, on T1-weighted images, heterogeneous signal intensity with a mixture of high and low signal intensities on T2-weighted images, and a contrast effect after gadolinium administration (Fig. 3). In some cases, it may be difficult to distinguish TSGCT from fibromatoses, granuloma, cystic lesions such as hematoma and abscess, and soft tissue sarcomas such as clear cell sarcoma16.

d. Fine needle aspiration cytology findings
Fine needle aspiration cytology is useful for diagnosis of TSGCT38,49,51. The typical cytology of TSGCT includes a large number of mononuclear stromal cells, foam cells, and a few multinucleated giant cells (Fig. 4), all of which correspond with histopathology findings.28,51 Accordingly, if clinical features are considered in conjunction with fine needle aspiration cytology findings, it is possible to diagnose TSGCT on the basis of cytology findings.51,53.

2. Surgical Preparation and Planning
a. Evaluation of lesion extent on MRI
MRI is useful for evaluating tumor spread in subcutaneous tissue and the extent of spread around bone, because the contrast between the lesion and adjacent tissue is excellent.16,50 In an MRI evaluation of lesion area in 23 cases of TSGCT, the mean surrounding occupancy range

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Fig. 2 A lateral radiograph showing erosion of the proximal phalanx of the thumb, caused by pressure from a tenosynovial giant cell tumor (arrow).

Fig. 3 Magnetic resonance images of a tenosynovial giant cell tumor of the little finger (arrows). The tumor exhibits relatively low signal intensity on a T1-weighted image and a contrast effect after gadolinium administration. a: T1-weighted image, b: T2-weighted image, c: T1-weighted image after gadolinium administration.

Fig. 4 Fine needle aspiration cytology of a tenosynovial giant cell tumor showing multinucleated giant cells (arrow), oblong mononuclear cells (small arrow), and histiocytic cells (arrowhead) on Papanicolaou staining (original magnification, 400×).
of the phalange in horizontal sections was 169°, and lesions surrounded the entire circumference of the bone in 3 cases.

b. Use of anesthesia, a tourniquet, surgical loupe, and surgical microscopy

A tourniquet should be used to determine the hemostasis area, and adequate anesthesia should be administered. A surgical loupe or surgical microscope is useful for preventing tumor remnants and for treating digital nerves and vessels. No recurrence was reported in 7 patients after diffuse giant cell tumors of the tendon sheath of the hand were removed with a surgical microscope.

c. Surgeon characteristics

Well-trained surgeons should perform treatment. For complete resection, it is necessary to have a thorough understanding of the nature of TSGCT and to have the specialized knowledge, experience, and skills for performing hand surgery, including expanding the operative field and performing reconstruction after excision.

3. Surgical Procedure

a. Incision

For a giant cell tumor of the tendon sheath in the fingers, a Brunner’s volar zig-zag incision, lateral midline incision, or dorsal longitudinal or transverse incision is made. Depending on the extent of the lesion, 2 palmar and dorsal incisions may be required.

b. Resection and reconstruction

When a lesion is detected on the palmar side, the digital nerves and vessels must be identified after making the incision. Moreover, if the lesion involves the neurovascular bundle, it needs to be isolated carefully. TSGCT lesions are usually almost completely covered with thin pseudocapsules and are clearly demarcated from the surrounding tissue, so they can be excised as a single unit that includes the pseudocapsules. However, when the lesion adheres to surrounding tissues, such as the tendon sheath, joint capsule, ligament, tendon, palmar plate, and skin, remnants of the lesion may remain when separating the lesion from the adhered tissue; therefore, the lesion should be resected along with approximately 1 mm of healthy tissue surrounding the adhesion site. In addition, there may be satellite lesions near the tumor, so careful dissection and observation of the color of the surrounding tissue are important.

When the lesion lightly compresses the phalange, the lesion is resected along with the adhering peristeum. When a deep depression is observed in the phalange, it is necessary to cauterize the surface of the depression via electrocautery and perform curettage after excising the lesion. Booth et al. used 0.25% phenol for treatment after curettage of the lesion. In addition, bone grafting may be needed after lesion removal when destructive bone changes are observed with cortical perforation and intrasosseous infiltration. If bone changes are noted on the attachment of the tendon, it may be necessary to cut the tendon and perform reconstruction.

It is difficult to obtain a sufficiently large margin for the surgical field in the DIP joint, because the tension of the soft tissue is high and the nail matrix is present. For dorsal lesions in the DIP joint, the lesion usually spreads in the proximal direction as it involves the terminal tendon; therefore, care must be taken at the time of resection, and it may be necessary to reconstruct the terminal tendon. In patients with osteoarthritis, the bony spur may need to be removed to improve curative potential. Joint fixation is rarely needed. Moreover, lesions on the dorsal side of the proximal interphalangeal joint also spread proximally as they involve the central band; hence, the central band must be reconstructed if it is removed.

Extensive incision is required for diffuse TSGCT and multicentric TSGCT in the fingers. The entire interior part of the tendon sheath or joint is opened, and the synovial membrane is removed to the maximum extent possible, unlike the procedure performed for localized tumors.

If important tissue needs to be sacrificed during complete resection of the tumor, additional reconstructive procedures and adequate postoperative care and rehabilitation are required. The patient should also be given instruction regarding adequate preoperative and postoperative local care and rehabilitation.

4. Adjuvant Therapy

Several studies have evaluated the effectiveness of radiation therapy for TSGCT. However, although radiation therapy is not usually recommended, owing to the high cure rate of surgery for TSGCT in the hand and the potential complications of radiation therapy, it may be recommended for some cases, such as progressive TSGCT cases that require amputation.

One patient with TSGCT showed a complete response after treatment with imatinib, a CSF1 receptor inhibitor. Moreover, international clinical trials of CSF1 receptor inhibitors are ongoing for TSGCT cases that are difficult to treat with surgery, mainly diffuse-type TSGCT, and some trials have been completed (https://clinicaltrials.gov/). These new medications are likely to offer useful treat-
ment options in the future.

**Conclusion**

Although TSGCT is a benign tumor, the rate of postoperative recurrence is high. The main cause of recurrence appears to be incomplete resection. Complete tumor resection requires accurate preoperative diagnosis, thorough surgical preparation and planning, and careful surgery. In the future, owing to advances in molecular biology, it would be ideal to treat TSGCT with safe and effective drug therapy. However, there are many challenges to overcome, such as elucidating the pathological conditions and suppressing drug complications.

**Conflict of Interest:** The Authors declare no conflict of interest.

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