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REVIEW ARTICLE

Giant cell tumor of tendon sheath in the pediatric population – review

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Abstract

Giant cell tumor of tendon sheath is a rare and benign soft-tissue tumor, which is even less common in the pediatric population. It may be connected with chromosomal translocations, often the 1p11-13. Symptoms include pain, swelling, palpable mass or limited range of motion. Magnetic resonance is the diagnostic method of choice. Histopathological image obtained from biopsy should be also evaluated. The gold standard of treatment is total surgical resection of the tumor, as incomplete excision may result in recurrence. Physicians should also consider the future function of the affected joint or limb. Our aim was to review the available literature about GCTTS in the pediatric population.

Keywords: orthopedics · pediatric oncology · giant cell tumor of tendon sheath

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Introduction

Giant cell tumor of tendon sheath (GCTTS), also known as tenosynovial giant cell tumor, is the most frequent form of giant cell tumors and the second most common soft tissue tumor of the hand (after ganglion cyst) [1-3]. GCTTS is most often localized in the hands [4]. This tumor originates from the sheath, bursa or joints [2, 5-6]. Tumor is typically benign, but with aggressive or malignant potential [2, 4]. GCTTS may occur as localized or diffuse form [7-8] and is most common among adults 30 to 50 years of age. [2, 4, 7, 9-10]. The global incidence rate of GCTTS located in the digits, limb and

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the diffuse-type are respectively 29, 10, and 4 per million person-years [11]. GCTTS is even less common in the pediatric population, with an incidence rate of 2.42 and 1.09 per million person-years in case of localized and diffuse tumors, respectively [12]. The knowledge about pediatric GCTTS is scattered across case reports and case series [7, 13]. Our aim was to review the available literature about GCTTS in the pediatric population.

Material and methods

For the purpose of this narrative review, we searched the PubMed database for articles in English and Polish language regarding GCTTS. The keywords "giant cell tumor of tendon sheath" or "giant cell tumor of tendon sheath pediatric" were used. We focused on articles published in the years 2016 to 2023. Evaluation was based on articles' titles and abstracts. Main criterium of including the papers to the review was if they concerned pediatric population. After evaluation of abstracts, full-text articles were analyzed, including the references cited.

Results

We found a total of 37 articles, including review articles, case series and case reports from the field of oncology, orthopaedics and radiology. After evaluation, 13 articles were included in our review. The rest of the articles were about adult patients. Cases reports are briefly summarized in the "Pediatric cases of GCTTS" section of this article.

Pathology

GCTTS is mostly located in the hand. Interphalangeal joints are often affected [13]. It may also be found in foot (with tendency to be spotted in forefoot), ankle, knee, hip, elbow or shoulder, although location in large joints or the spine is rare [2, 4]. This tumor can be divided into two types: intra-articular or extra-articular [7]. GCTTS may be described as localized tumor, which tends to be a benign form, and diffuse form, which appears to be more aggressive and more likely to localize in large joins [4]. Local and diffuse forms are morphologically ndistinguishable, however location near large joints or local agressiveness are more characteristic for the diffuse form [13]. The origin of GCTTS is uncertain and the hypothesised pathomechanism involves an inflammatory reaction followed by regenerative hyperplasia or local lipid metabolism abnormality [1, 7]. Recent studies revealed that there may be a connection with giant cell tumors and chromosomal translocations involving short arms of chromosome 1, which are present in most cases of GCTTS [1, 13]. These rearrangements often involve 1p11-13, t(1;2)(p11;q35–36) or translocations of 16q24 [13-14]. It is noteworthy that 1p13 is a location of CSF1 – Colony Stimulating Factor 1. COL6A3 – collagen 6A3 promoter element is located at 2q37 [8, 14]. Regular CFS1 function is stimulating secretion of macrophage colonies. These translocations result in prolonged lifetime of the CSF1 mRNA and its local over-expression, leading to an inflammatory infiltration of mononuclear and multinuclear giant-cell osteoclasts and macrophages [10, 14-15]. This situation, known as „the landscape effect" leads to the fact that only stromal cells present neoplastic mutation, and infiltration of osteoclasts is a reactive element [14]. Therefore GTCCS can be described as mixed disease: neoplasmatic and inflammatory [16].

Macroscopically, GCTTS is usually a 1-3.5 cm tumor with fibrous capsule [17]. In some cases, these tumors may present different colors – grey, yellow-orange, brown-ish – as a result of different composition and amount of hemosiderin, fibrin, collagen and histiocytes inside [16, 18].

Microscopic images of GCTTS show macrophage-like cells, which can be described as spindled or polyhedral, synovial cells and osteoblastic multinucleated giant cells. Synovial cells may appear as proliferating. Cells may contain hemosiderin deposits [4, 17] Some cases may contain xanthoma cells, hyalinization or inflammation factors, ferruginous phagocytes and collagen matrix [7, 16-17]. According to the literature, only 2-16% of cells present neoplastic transformation, and the majority appears as reactive, but not transformed cells [14]. Tumors may appear as lobulated, surrounded by collagen [7]. Malignant forms present tumor necrosis, infiltrative pattern, prominent nucleoli and high nuclear to cytoplasmic ratio. Shape is round to oval. Cells are mostly mononuclear, and may contain up to 5 mitoses per 10 high power fields It is vital to take under consideration the fact that both malignant and benign cells contain apoptotic figures and mitosis [13]. Malignant forms tend to infliltrate local structures, such as muscle, tendon or adipose tissue [13].

Clinical presentation

As the typical patient with GCTTS is 30 to 50 years of age, this is a rare disease in the pediatric population, but its symptoms seem to be similiar in both populations [13, 18]. The clinical presentation may vary, depending on tumor location. Tumor may appear as intra or extra-articular [7, 14]. When located in the hand, the GCTTS is usually an asymptomatic, painless, slow-growing and firm mass, frequently located on the palmar side [4, 16]. Sometimes it may cause swelling or periarticular effusion [4]. Pain and swelling are characteristic for the intra-articular location. When this tumor is located in hip joint, pain is the main symptom, with reduced swelling [14]. Among the significantly less frequent symptoms are: reduced range of motion in the joint, instability or locking of the joint, increased warmth of skin in the are of the affected joint. The extra-articular

presentation is usually associated with pain and noticeable tumor mass, while the swelling or joint malfunction appear significatly less often [14]. When located in the digits, the clinical picture may include mobility disfunction or pain [16]. Symptoms are usually present for 10 months to 3 years [14]. GCTTS may appear as a main tumor with satelitary tumors located a few milimeters away from it [4, 16]. GCTTS of the knee may present similarly to meniscal syndrome [4, 14]. Tumor located in the spine is extremely rare, but may cause neck, shoulder or back pain, nerve root compression symptoms and limb disfunction, which are dependent on tumor size. [2].

According to Al-Qattan's classification, there are two types of GCTTS:

- **type 1** – single tumor surrounded by a round or lobulated capsule of various thickness;
- **type 2** – multiple separate tumors without clearly marked capsule [1, 16].

Type 2 is described as having higher recurrence rates than type 1 [1, 16].

Differential diagnosis should contain ganglion cysts, lipomas, inclusion cysts, fibromas, rheumatoid nodules, synovial sarcoma, pigmented villonodular synovitis or inflammation of tendon sheath, all of which may be easily diagnosed microscopically [13].

Diagnostic methods

Magnetic resonance imaging (MRI), regarded as diagnostic method of choice, allows to recognize precisely how the tumor is affecting its surroundings(e.g. nerves, joints or veins). It is also helpful when segregating tumors to types 1 and 2 in Al-Qattan classification. MRI can be also used as a tool to plan surgical treatment. Tumors appear as structures connected with tendon and its sheath, which is pathognomonic for GCTTS [1, 16, 19-21]. MRI scans of intra-articular tumors can also reveal joint effusion, synovial hypertrophy or pressure erosions [22]. Localized forms are well-defined, while diffuse forms usually appear as located in joints and associated with its effusion. Hemosiderin deposits present in some tumors are connected with weak to intermediate T1 and T2 signals, with enhancement after gadolinium injection [2, 19]. Nguyen et al. reported, that in MRI scans of 24 children, most of them presented joint effusion signs, and it was significantly more frequent in patients with diffuse type of tumor [22].

In X-ray images it is possible to notice the impression of a growing tumor on bone, particularly in the phalanges. Erosion of cortical bone, degenerative lesions, cystic erosions or soft-tissue masses may be also described [1, 2, 10, 16].

Doppler ultrasonography allows assessment of the tumor's vascularization. In most cases GCTTS is not vascularized [16, 19-20]. Ultrasound-guided fine needle aspiration and cytology may also be performed as a part of the diagnostic process because in most cases its results correspond with histopathology findings [19, 21].

Treatment options

The gold standard of GCTTS treatment is total resection surgery with a careful preservation of tendons, arteries, veins and nerves in the local area of the lesion [1, 14]. In localized tumors a single surgical procedure is usually sufficient. If applicable, arthroscopy should be the method of choice, as it reduces morbidity and recurrence rate [14]. Diffuse GCTTS usually requires surgical excision. It may be problematic to obtain total resection of affected tissue, so recurrences may appear more frequently [14]. The most important issues regarding surgical management are joint damage, loss of function and recurrence [1, 7]. Risk factors of GCTTS recurrence are presented in Table 1 [1, 4, 16, 23].

Table 1. Risk factors of GTCCS recurrence

Most common risk factors of giant cell tumor of tendon sheath recurrence
• Incomplete excision • Joint or bone involvement • Type 2 (Al-Qattan classification) • Presence of mitotic figures • Male gender • Tumor size > 20 mm • History of GCTTS recurrence • Tumor's histological image

Cases of incomplete resection may need post-operative radiotherapy, to avoid recurrence lesions, according to Gouin et al. [19]. Radiotherapy may be applied as an external beam or intra-articular injection of radioactive isotopes [14].

The ENLIVEN study published in 2016 demonstrated that oral doses of pexidartinib (inhibitor of the colony stimulating factor 1 receptor, CSF1R) is effective in treating GCTTS. It is noteworthy that this study included only patients above 18 years of age and at this moment there are no published articles regarding its use in the pediatric population [12, 14, 23-24].

Pediatric cases of GCTTS

As noted earlier, GCTTS is indeed a rare disease in the pediatric population. In Table 2 we summarised selected case reports published in the literature [2, 13, 25-32].

In their study of 26 patients with GCTTS of foot and ankle, Cevik et al. included 6 children (see the summary in Table 3) [23].

Table 2. Selected pediatric cases of GCTTS summarized

Study	Number of cases	Sex	Location	Summary
Tsui et al. [27]	1	F	Spine	• Spinal GCTTS of C1-C2 joint co-existing with medulloblastoma • no resection due to lack of symptoms and technical difficulties
Mastboom et al. [6, 11]	76	39 F 37 M	Mostly big joints – knee, ankle, wrist	• 29 cases of localized type • 38 cases of diffuse type • 9 unknown cases
Zeng et al. [2]	2	F	Spine	• symptoms included weakness and numbness of limbs • total resection was performed
Occhipitini et al. [13]	2	M, F	Toes	• male patient had tetraploidy and chromosomal rearrangements • female patient had normal karyotype
Ansari et al. [26]	3	F	Fingers	• no bone erosion • resection was performed
Meyers et al. [28]	1	M	Mandible and multiple joints	• coexistance with Noonan syndrome • Noonan syndrome is known to be connected with mandibular GCTTS, but it rarely occurs in other multiple joints
Shukla et al. [29]	1	M	Proximal phalanx of middle finger	• no trauma history; painless swelling of proximal phalanx • no bony erosion
Mankuzhy et al. [30]	1	F	Thigh	• KRAS p.G12D mutation • overexpression of CSF1R • diffuse type of GCTTS
Yun et al. [31]	1	M	Shoulder	• mass originating from the deltoid muscle • intramuscular, diffuse type of GCTTS
Cho et al. [32]	1	F	Neck	• tumor originating from the occipital condyle with erosion of the skull and atlas • total resection of the mass with condylectomy, partial laminectomy of atlas and suboccipital craniectomy were performed

Table 3. Clinical details of pediatric patients with GCTTS located in foot and ankle according to Cevik et al.

Age	Sex	Size [cm]	Symptoms duration	Pre-operative diagnosis	Type	Recurrence after surgery
11	M	1 x 1 x 0.5	3 months	Ganglion	Localized	No
15	F	2 x 1.8 x 1.5	5 years	None	Localized	No
8	F	6 x 3 x 3	4 years	Hemangioma	Localized	No
8	F	4.5 x 3 x 2	2 years	GCTTS	Localized	Yes
17	M	4.4 x 3.5 x 2	2 years	None	Diffuse	No
10	F	3.5 x 1.5 x 0.7	3 years	Schwannoma	Localized	No

Their analysis revealed that most of the children presented symptoms for a few years before being diagnosed and surgically treated and pre-operative diagnoses were mostly wrong, only one patient was diagnosed correctly. Five out of 6 children with GCTTS had a localized type of tumor, and one had a diffuse type. Five of them did not present signs of recurrence after a follow up, and one female patient with a localized type of tumor manifested recurrence symptoms after 24 months, due to incomplete resection. There was no recurrence after re-operation. [23].

There are case reports describing GCTTS mimicking septic arthritis. This clinical situation is uncommon, but should be taken into consideration, as it may lead to unnecessary or inadequate surgical intervention [33-34]. According to the literature, such cases may be applicable in pediatric population, especially in patients with locomotory disfunctions and elevated inflammatory markers.

Conclusions

Giant cell tumor of tendon sheath is relatively rare disease among adults, and even more rare in pediatric population. Pexidartinib appears promising in the treatment of GCTTS, however the ENLIVEN study did not include the assessment of its effect on children. It is worth remembering, that the knowlegde about GCTTS is still limited and there is a need for diagnostic and therapeutic recommendations.

Funding

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Conflicts of interests

None.

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