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PRIMARY TUMOR (TUMORAL) CALCIFICATION IS A RARE DISEASE IN THE PRACTICE OF A RHEUMATOLOGIST AND ORTHOPEDIST: EXPERIENCE WITH THE USE OF AN INTERLEUKIN-1 INHIBITOR IN COMBINATION WITH SURGICAL CORRECTION

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Background. Primary tumoral calcinosis is an orphan disease. There are few data in the literature on the incidence of this disease, as well as clinical recommendations for treatment.
Clinical case. This report presents the case of an 11.5-year-old boy with primary tumoral calcinosis and equinus deformity of the foot. The patient had multiple foci of the subcutaneal calcification, cannot walk, experienced fatigue, and had high fever and equinus deformity of the left foot. Immunological and genetic studies were performed, but any specific mutations were not found. After the diagnosis was verified and interleukin-1β inhibitor therapy was prescribed, there was a significant positive trend observed in the patient: a significant improvement in the patient's general condition, a decrease in the number of calcinates, and a reduction in inflammation. Calcification of the Achilles tendon and gastrocnemius muscle was the cause of the deformity of the left foot.
Discussion. Significant improvement was achieved during treatment: the boy started walking, fatigue was decreased, no new calcificates were formed, and inflammation was under the control. Using an inhibitor of interleukin-1β as a permanent therapy of primary tumoral calcification allowed performsurgical treatment without complications from an operation site, as well as a relapse of deformity.
Conclusion. The clinical case presented here demonstrated the application of an interdisciplinary approach to the treatment of an extremely rare disease.

Keywords: primary tumor calcification; tumoral calcification; familial tumoral calcification; hyperphosphatemic hyperostosis syndrome; canakinumab; equinus deformity; clinical case.

ПЕРВИЧНЫЙ ОПУХОЛЕВЫЙ (ТУМОРАЛЬНЫЙ) КАЛЬЦИНОЗ — РЕДКОЕ ЗАБОЛЕВАНИЕ В ПРАКТИКЕ РЕВМАТОЛОГА И ОРТОПЕДА: ОПЫТ ПРИМЕНЕНИЯ ИНГИБИТОРА ИНТЕРЛЕЙКИНА-1 В СОЧЕТАНИИ С ХИРУРГИЧЕСКОЙ КОРРЕКЦИЕЙ

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Обоснование. Первичный опухолевый кальциноз является крайне редким заболеванием. Статистические данные о встречаемости данной патологии, а также клинические рекомендации по лечению в русскоязычной литературе отсутствуют.
Клиническое наблюдение. Представлен клинический случай лечения пациента 11,5 года с первичным опухолевым кальцинозом и эквинусной деформацией левой стопы. Ребенок поступил с жалобами на наличие

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множественных подкожных кальцинатов, невозможность самостоятельно ходить, утомляемость, подъем температуры до фебрильных цифр, деформацию левой стопы. Проведен комплекс клинико-лабораторного, иммунологического и генетического обследования. После установки диагноза и назначения терапии ингибитором интерлейкина-1β отмечена значительная положительная динамика: общее состояние пациента существенно улучшилось, уменьшилось количество кальцинатов, были купированы воспалительные явления. При обследовании обнаружено, что деформация левой стопы обусловлена кальцификацией ахиллова сухожилия и икроножной мышцы. Для лечения деформации стопы было успешно применено хирургическое лечение.

Обсуждение. В результате комплексного подхода к лечению достигнуто значимое клиническое улучшение. Ребенок самостоятельно ходит, прекратилось образование новых кальцинатов, снизилась утомляемость, был купирован воспалительный процесс. Благодаря применению ингибитора интерлейкина-1β в качестве постоянной терапии первичного опухолевого кальциноза удалось выполнить хирургическое лечение без осложнений со стороны послеоперационной раны, а также предотвратить рецидив деформации.

Заключение. Представленный клинический случай демонстрирует применение междисциплинарного подхода к лечению крайне редкого заболевания. При отсутствии клинических рекомендаций по лечению и диагностике первичного опухолевого кальциноза верификация правильного диагноза и применение комплексного лечения позволили добиться значительного улучшения качества жизни пациента. Мы считаем необходимым сообщить не только о новых эффективных методах лечения, но и информировать специалистов о клинической картине столь редкого заболевания.

Ключевые слова: первичный опухолевый кальциноз; туморальный кальциноз; семейный туморальный кальциноз; гиперфосфатемический гиперостоз-синдром; ингибитор интерлейкина-1β; канакинумаб; эквинусная деформация; клинический случай.

Background

Primary tumoral calcinosis is characterized by deposits of calcium and phosphorus salts in subcutaneous fat tissue [1]. Calcinosis manifests as nodule-shaped, densely calcined masses localized in soft tissues; typically, on the extensor surface of joints [2]. This condition was first described in foreign literature in 1898 [3]. In 1943, Inclan summarized the available data and compared the results of his own observations to clarify the condition as an independent disease, defined by the term "tumoral calcinosis" [4]. In 1960, the familial nature of this disease was established [5]. Tumoral calcinosis is generally progressive in nature and is also known as primary tumoral calcinosis, familial tumoral calcinosis, and hyperphosphatemic hyperostosis syndrome. Several types of tumoral calcinosis have been identified, defined by specific laboratory parameters. Type I is characterized by hyperphosphatemia, tooth abnormalities, and elevated levels of 1.25-dihydroxyvitamin D ($1.25[OH]_2D$) while type II develops in patients receiving renal replacement therapy with hemodialysis. Type III is a familial type involving hyperphosphatemia but normal levels of $1.25(OH)_2D$ [2, 6]. Genetic studies have identified mutations in *GALNT3*, *Klotho*, and *FGF23* that lead to the development of tumoral calcinosis. Pathogenesis of tumoral calcinosis is usually based on dysregulation of phosphorus homeostasis. Mutations that cause familial tumoral calcinosis or hyperphosphatemia-hyperostosis syndrome do so due to the relative insufficiency or resistance FGF23 cleavage. This molecule is the primary regulator of phosphorus levels; thus, hyperphosphatemia arises due to increased renal tubular reabsorption of phosphate and increased or inadequate production of $1.25(OH)_2D$. Gastrointestinal absorption of phosphorus and calcium is consequently enhanced, in turn leading to hyperphosphatemia. Nodules of ectopic calcinosis and/or diaphyseal hyperostosis develop, which can manifest as pain in the diaphysis of the long bones and is often mistakenly diagnosed as osteomyelitis [7]. The mechanisms underlying the involvement of hyperphosphatemia in tumoral calcinosis are yet to be elucidated. Cases of tumoral calcinosis with normal indicators of phosphorus metabolism have been described, as have cases with no gene mutations in the relevant genes. This indicates that there may be multiple mechanisms of disease development [8].

Clinical aspects of the disease include early age of onset and periarticular tumor lesions which restrict movement. The lesions are painless and displaced upon palpation, and the white calcareous contents can be identified by puncture or biopsy of the lesions.

In terms of imaging findings, X-ray is used to identify focal calcinosis in soft tissues, which merge into cysts and are most often located on extensor

surfaces. Computed tomography (CT) data can be used to identify focal calcinosis, in the form of cysts, which communicate with the synovial membrane. Magnetic resonance imaging (MRI), T1-weighted imaging reveals non-homogeneous lesions with a low-intensity signal and T2-weighted images reveal low-intensity diffuse signals which imply bright nodules alternating between intense signal and no signal.

The most characteristic laboratory abnormalities are hyperphosphatemia (and, less commonly, normophosphatemia), normocalcemia, normal $1.25(OH)_2D$ levels, normal parathyroid hormone levels, normal glomerular filtration rate, and lack of autoantibodies (such as antinuclear factor and antibodies to scleroderma, dermatomyositis, or extractable nuclear antigens).

Morphological examination or patients with tumoral calcinosis typically reveals ectopic calcification with chronic inflammation and multiple foamy macrophages, as well as the presence of a capsule and multinucleate giant cells.

This study aimed to highlight the characteristics of an ultra-rare orphan pathology, tumoral calcinosis, and demonstrate the application of an interdisciplinary approach (drugs and orthopedic correction).

Clinical case

Boy R., 11.5 years old, presented with calcification in the lower extremities — mainly in the buttocks — inability to walk, rapid fatigability, weakness, daily rise in body temperature to febrile numbers, and inflammatory activity in blood tests (C-reactive protein [CRP] levels of >200 mg/l, erythrocyte sedimentation rate of 60–70 mm/h). Indicators of calcium and phosphorus metabolism were within the normal range.

The patient had been sick since he was 3.5 years old (November 2009), when weight loss was first noted and weakness, knee-joint pain, and densification under the skin appeared. The area and degree of densification increased. In May 2010, biopsy of the lesions was performed along the anterior surface of the legs. Morphological studies indicated the changes to be "soft-tissue calcification". In December 2011, a viral infection caused aggravation of the condition, with muscle weakness, rapid fatigability and muscle pain reported. From 2012–2016, the patient was regularly examined in one of the federal rheumatological clinics in Moscow, where juvenile dermatomyositis was diagnosed. The child was subsequently treated with corticosteroids and methotrexate with no significant positive change except for relief of fever and inflammatory activity during corticosteroid treatment. Immunological examination detected no autoantibodies. No signs of myocytolysis were detected; creatine phosphokinase, lactate dehydrogenase, and aspartate aminotransferase activities were within the normal range, and electroneuromyography indices showed no abnormalities.

At the time of the first hospitalization in December 2016, multiple calcification was found in the lower extremities, mainly the buttocks, knee joints and front surfaces of the lower legs, as well as in the subcutaneous tissue on the posterior surface of the thigh. The volume of tissue in the buttock area was increased, and the buttocks had stone-like density. Specific facial features, including lipoatrophy and signs of exogenous hypercorticoidism, were observed. The patient had signs of a markedly inadequate diet, as the subcutaneous fat layer on the face, trunk, and limbs was thin. Deformity of the locomotor system was observed along with impaired growth of the left lower limb and physical development, severe damage to the muscular system, muscle hypotrophy, and multiple contractures of the upper- and lower-extremity joints. The range of motion in the temporomandibular joint was limited and hyperthermia was noted periodically over densified areas. The patient received systemic glucocorticosteroid therapy and methotrexate for many years.

Immunological blood tests revealed the patient to be negative for antinuclear factor and antibodies in polymyositis were as follows: Mi-2, Ku, PM-Scl100, PM-Scl175, signal-recognition particle, and antisynthetase (Jo-1, PL-7, PL-12, EJ, OJ). Antibodies to extractable nuclear antigens were not detected. An X-ray examination revealed numerous, large, irregularly shaped areas of calcification in the upper and lower extremities. Whole-body MRI revealed extensive zones of heterogeneous MR signal on the projection of gluteal muscles on both sides (alternating hypo-/hyper-intensive MR signals). Multiple calcifications were observed on CT images. The appearance of the lower extremities and CT data are presented in Fig. 1. Morphological investigation of the muscle biopsy revealed that the muscle tissue contained layers of edematous fibrous connective tissue, and muscle fibers were thick with dystrophic changes. Biopsy of the calcified

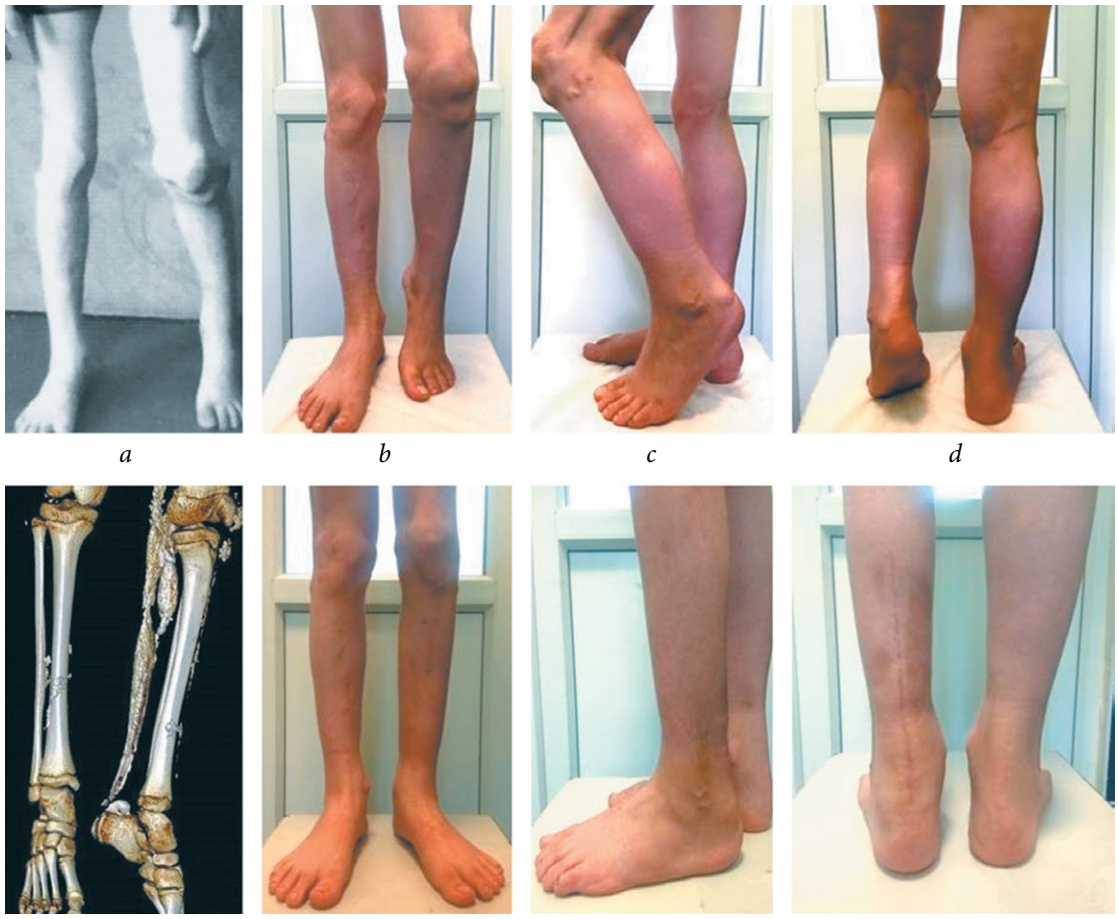
area revealed diffuse stripe-shaped lymphocytic macrophage infiltration with a large number of "foreign body" multinucleated cells. Foam cells were present, and calcification was delimited by the capsule. Differential diagnoses of juvenile dermatomyositis and polymyositis, chronic kidney disease, synovial chondromatosis, calcific myositis, bursitis, tendonitis, and diseases accompanied by calcium and phosphorus metabolic disorder were investigated. Molecular genetic testing involving sequencing of the complete coding regions of the *GALNT3*, *FGF23*, and *Klotho* genes identified no mutations. Thus, a new generation, exome-wide association study was carried out using the Illumina platform. No clinically significant variants of the aforementioned genes were found, nor were any pathogenic mutations identified in the genes involved in phosphorus and calcium metabolism.

Given the presence of fever and high level of CRP (202 mg/l; normal values are <5.0 mg/l), recurrence of fever upon reduction of the dose of systemic glucocorticosteroids (corticosteroid dependence), an interleukin-1β inhibitor, canakinumab, was administered. This approach was selected based on the presence of symptoms of autoinflammation (fever, high CRP, and positive effects of high doses of systemic corticosteroids), as well as the reported utility of interleukin-1 inhibitors (anakinra and canakinumab) presented by a group of researchers from the U.S. National Institute of Health (Bethesda) [2]. Canakinumab therapy (prescribed in accordance with the decision of the medical board and Federal Law No. 323 after obtaining informed consent from the patient's parents) was administered subcutaneously at a dose of 150 mg (4 mg/kg) every 4 weeks. At this point, the fever was eliminated, CRP levels were normalized to 0.2 mg/l, and the patient was able to move independently, which he could not prior to admission. Administration of systemic corticosteroid was gradually ceased. Indicators of calcium and phosphorus metabolism remained within the normal range. For the >2-year follow-up period, during which canakinumab therapy was continued, new or increased calcification was not observed; furthermore, regression of existing calcification was noted (decreased volume and density). Canakinumab therapy is being continued presently.

The patient exhibited a movement pattern of weight-bearing on the front section of the left foot due to equinus deformity, and a fixed position of the left foot in plantar flexion (150°). Passive correction was possible up to 145°. Multiple calcifications were identified in the area of the knee joints and posterior surfaces of the lower legs and hips. A bone density of 10×20 mm was determined by palpation along the lateral surface of the Achilles tendon. According to X-ray investigations, multiple soft-tissue calcifications were present (more so on the left-hand side); the Achilles tendon, tendon of the gastrocnemius muscle, and lower third of the gastrocnemius muscle were calcified (Fig. 1).

The patient underwent surgical correction of orthopedic changes that occurred due to the shortening of the right lower limb. Surgery was performed under anesthesia in the supine position. An incision was made along the posterior surface of the left lower leg along the projection of the Achilles tendon and the loose subcutaneous fat was dissected. The tibial fascia and tissue of the Achilles tendon sheath could not be differentiated due to their intimate fusion. The tendon sheath and Achilles tendon appeared as a single conglomerate of whitish color with inclusions of dense calcifications of various size, surrounded by scar adhesions with adjacent soft tissues. The conglomerate was isolated from the soft-tissue adhesions to improve the effect of the planned myoplasty with myogaster of the gastrocnemius muscle. This conglomerate wall opened spontaneously in the area of the posterior surface when isolation of the Achilles tendon conglomerate from the fibrous adhesions was attempted. When slight pressure was applied to the area of the hole, liquid content of the conglomerate — which was a uniform whitish mass with a density resembling liquid sour cream or lime solution — flowed into the wound (Fig. 2).

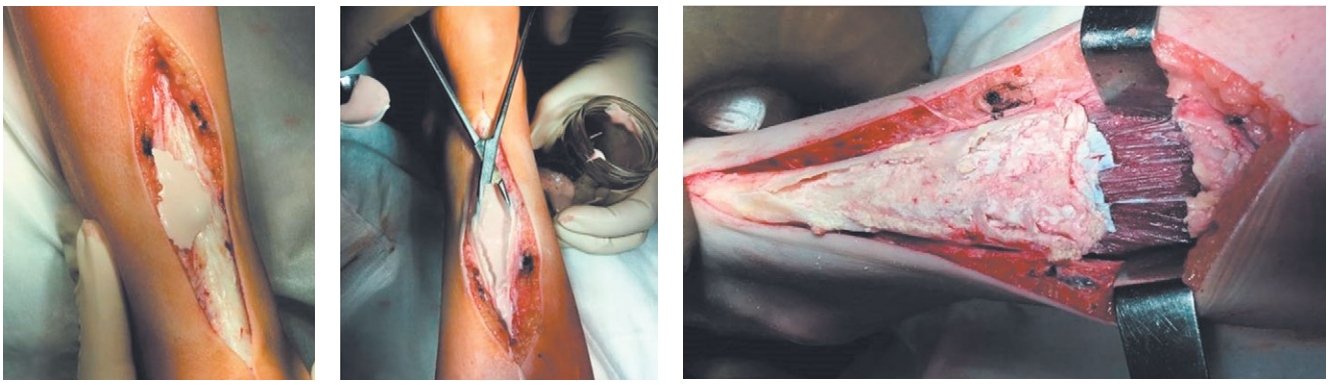
Solid particles of various sizes could be felt within the liquid, with a density resembling crystals or grains of sand. When the cavity was opened, about 20 ml of liquid was secreted. Review of the cavity revealed no tendon structures; the cavity was localized within the Achilles tendon itself, with the altered tendon tissue forming the cavity walls. The length of the cavity corresponded to the length of the Achilles tendon, reaching the extensor expansion of the gastrocnemius muscle and spreading proximally to the muscle mass. The proximal border of the cavity was not palpable and regions of calcification of various sizes were



a *b* *c* *d*

e *f* *g* *h*

Fig. 1. Images illustrating the pre- and postoperative characteristics of a patient with tumoral calcinosis. *a* — appearance of the patient at 7 years old (2013). Calcinosis was observed in the knee joints, and equinus deformity of the left foot was identified; *b–d* — photograph of the patient at 11.5 years old (2017). Multiple areas of calcinosis were observed in the knee and ankle joints, and equinus deformity of the left foot was identified; *e* — multispiral computed tomography images of the lower legs, performed in 2017, reveal multiple areas of soft-tissue calcinosis in the lower legs. This is more obvious on the left side. The Achilles tendon and gastrocnemius muscle appear calcified and partially calcified, respectively. *f–h* — photograph of the patient 3 months after surgical treatment. The equinus deformity of the left foot has been corrected and no new calcifications are seen



a *b* *c*

Fig. 2. Image illustrating the intraoperative changes of a patient with tumoral calcinosis. *a* — operative photograph of the wound at the time of spontaneous opening of the tissue conglomerate wall in the region of the Achilles tendon; *b* — the cavity in the Achilles tendon was opened revealing whitish liquid content; *c* — view of the intraoperative wound after myoplasty. Gastrocnemius muscle fibers are unchanged

noted on the cavity walls. The liquid contents of the cavity were completely removed and sent for morphological examination together with sections of the fibrous conglomerate wall. The cavities of the Achilles tendon and the proximal lower leg were repeatedly washed with isotonic sodium chloride solution and Furacilin solution, then the gastrocnemius muscle myogaster was isolated.

Visually, the muscle tissue was unchanged. The myogaster muscle fibers were dissected in a checkerboard pattern (myoplasty) at a distance of 2 cm proximal to the border with the extensor expansion. The foot was replaced at a 90° angle. Posterior capsulotomy (capsulotomy of the ankle and talocalcaneal joints) was not performed as myoplasty appeared to be sufficiently successful. The medial and lateral edges of the Achilles tendon were tightly sutured so as to eliminate the cavity inside, and the wound sutured. Immobilization was achieved with a posterior plaster cast keeping the foot at 90°. The postoperative course was uneventful, antibacterial therapy was administered for ten days and dressings were applied. The wound healed by primary intention and sutures were removed on day 14 postoperatively. Prior to discharge, the left lower limb was immobilized from the middle third of the thigh to the toes with a circular plastic dressing.

Histological investigations revealed changes typical of tumoral calcinosis (Fig. 3).

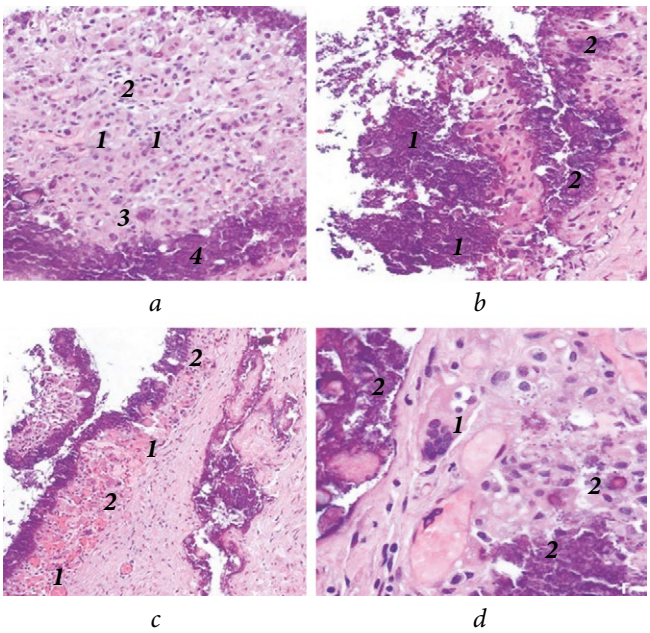


Fig. 3. Images illustrating the histological changes in a patient with primary tumoral calcinosis. *a* — representative images of the inflammatory infiltrate stained with hematoxylin and eosin at ×200 magnification showing (*1*) lymphoplasmacytic infiltration, (*2*) foam cells and macrophages, (*3*) multinucleate giant cells of foreign bodies, and (*4*) calcium salts (scale ×200); *b* — images of the cyst wall stained with hematoxylin and eosin and imaged at a magnification of ×200 revealed a large amount of calcium (*1*) in the wall and (*2*) in the lumen; *c* — images of the cyst wall with calcification stained with hematoxylin and eosin and imaged at a magnification of ×100 with calcium revealed (*1*) numerous full-blooded vessels and (*2*) lymphoplasmacytic infiltration; *d* — images of the cyst wall stained with hematoxylin and eosin and imaged at a magnification of ×400 revealed (*1*) multinucleate giant cells of foreign bodies and (*2*) calcium deposits

One month after surgery, immobilization was ceased and the patient underwent a course of physiotherapy and massage in a primary care facility. At the follow-up examination 3 months after surgery, the patient was able to walk with even loading on both lower limbs and biphasic gait. The left foot remained in the physiological position and active movements were possible within a range of 20°. The postoperative scar exhibited no signs of inflammation. Decreased calcinosis in the Achilles tendon was confirmed by X-ray of the left lower leg. The results of surgical treatment persisted throughout the year of follow-up. Images of pre- and postoperative findings are presented in Fig. 1.

Discussion

Primary tumoral calcinosis is an extremely rare condition, the true incidence of which is unknown. The most pronounced symptoms observed during follow up have been documented, and retrospectively used to defined diagnostic criteria for this disease.

Primary (familial) and secondary calcinosis are distinguished by their etiology; the former is an autosomal recessive disease associated with mutations in either *FGF23*, *Klotho-1*, or *GALNT3*, which regulate phosphorus homeostasis [2, 9–11]. Secondary tumoral calcinosis is a consequence of impaired renal function (calcinosis in chronic renal pathology) [12–14]. This condition develops in the context of immunopathological disease (dermatomyositis) [15] as well as phosphorus and calcium metabolism disorders [16, 17].

The clinical presentation of the current patient was characterized by a very long period prior to establishment of the diagnosis. The initial diagnosis of juvenile dermatomyositis was made despite the absence of typical manifestations such as skin lesions (heliotropic erythema, the Gottron sign, and so on), the presence of laboratory manifestations of myocytolysis, and typical changes in electroneuromyography. The patient did not respond to therapy for juvenile dermatomyositis and differential diagnosis was performed at our clinic to distinguish between inflammatory myopathies (juvenile dermatomyositis), ossifying progressive fibrodysplasia, calcifying myositis, and autoimmune and immune-proteosomal diseases. Immuno-proteosomal diseases, for which the molecular mechanisms have been reported, were ruled out by next-generation

sequencing. The mRNA level of interferon-dependent genes can be evaluated in order to diagnose or rule out immune-proteosomal disease with high accuracy; however, this was not investigated as the technique (Interferon score) is not available in the Russian Federation. Due to special aspects of the clinical presentation; namely, the radiological and morphological data; as well as the absence of symptoms of myocytolysis, tumoral calcinosis was diagnosed. An interesting feature of the present case is that the diagnosis could not be confirmed by molecular genetic methods; neither Sanger sequencing nor exome-wide analysis revealed mutations in relevant genes. It may be that a defect existed in a gene that has not been previously found to be associated with the phenotype and which triggers disease development through non-obvious pathogenetic mechanisms. Whole-genome sequencing; preferably of father, mother, and proband; may offer a solution to this issue. However, the absence of detected mutations may be related to technical aspects of next-generation sequencing, which does not always identify insertions and deletions reliably, as well as abnormalities of abundance. The laboratory findings and significant effects of administration of interleukin-1 blocker indicate that an auto-inflammatory mechanism (inflammasome activation) underlies the pathogenesis of this disease. Knowledge of the disease mechanism leads us to postulate that granuloma cells, as well as the giant multinucleated macrophages that surround regions of calcification, are the main producers of pro-inflammatory cytokines as is the case in gout, amianthosis, and other diseases with an auto-inflammatory component.

Conclusions

Primary tumoral calcinosis is an extremely rare disease for which conservative therapy and surgical correction approaches have not yet been developed. Differential diagnoses include rheumatic and metabolic diseases, as well as post-traumatic muscle changes.

Surgical treatment for systemic diseases is a subject of discussion and requires an unconventional approach. The outcome of surgical treatment is difficult to predict due to the lack of information on regeneration of altered tissues. Disease progression can lead to recurrence of deformities.

Treatment with an interleukin-1β blocker therapy proved to be effective and safe in the present case, and enabled surgical treatment to be performed. The outcome of surgery was successful with no recurrence of calcinosis observed in the surgical treatment zone.

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Ethical review. Written informed consent was obtained from the patient's legal representatives for the analysis and publication of medical data.

Contribution of the authors

V.V. Petukhova and *A.G. Veselov* wrote the article and collected and processed graphic material.

R.V. Idrisova, *L.S. Snegireva*, and *O.L. Krasnogorskaya* prepared clinical and laboratory material.

M.M. Kostik and *E.N. Suspitsyn* wrote sections of the article and edited the text of the article.

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