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Original article

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Evaluation of ankle joint synovitis in diabetic neuroosteoarthropathy in relation to an inflammatory phase of chronic osteomyelitis

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Abstract

Diabetic neuroosteoarthropathy complicated by osteomyelitis is one of the severe conditions of the ankle joint in patients with diabetes. The role of the synovium in the pathogenesis of this disease remains poorly understood. **Purpose** To identify structural changes in the synovium of the Charcot ankle depending on the inflammatory phase of chronic osteomyelitis. **Material and methods** The ynovium and osteochondral fragments of the ankle were studied in 33 patients. Paraffin sections stained according to the three-color Masson method, hematoxylin and eosin, and semi-thin sections stained with methylene blue and basic fuchsin were studied using an AxioScope. A1 microscope with an AxioCam digital camera (Carl Zeiss MicroImaging GmbH, Germany) and Zenblue software (Carl Zeiss MicroImaging GmbH, Germany). The phase of the inflammatory process of chronic osteomyelitis was assessed according to the HOES of Tiemann et al (2014) and synovitis according to Krenn et al (2006). **Results** Full-thickness articular cartilage defects, synovial pannus, foci of osteonecrosis in the subchondral zone, bone microsequesters, osteoclastic resorption of the subchondral bone plate, replacement of bone marrow structures with granulation tissue, the severity which depended on the inflammatory stage of chronic osteomyelitis, were recorded in the process of studying osteochondral fragments. In 82 % of patients, the inflammatory phase of chronic osteomyelitis was characterized as active and subacute. In all the cases, hyperplasia, hypervascularization and hyperemia of the synovium with the presence of bone and cartilage fragments were observed, as well as inflammatory infiltrate, synovial pannus invading the articular cartilage. The vessels featured a pronounced narrowing of the lumens or their complete closure. The severity of synovitis correlated positively with the inflammatory phase of chronic osteomyelitis; Spearman's correlation coefficient of 0.76 indicated high relationship. **Conclusions** In diabetic osteoarthropathy of the ankle joint complicated by chronic osteomyelitis, the irreversible structural changes revealed in the synovium contribute to the formation of synovial pannus and the progression of destruction of the articular cartilage and subchondral bone. The severity of synovitis positively correlates with the inflammatory phase of chronic osteomyelitis.

Keywords: Charcot osteoarthropathy, osteomyelitis, ankle joint, synovium, light microscopy

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INTRODUCTION

One of the most serious foot and ankle conditions in patients with diabetes mellitus and peripheral neuropathy is diabetic neuroosteoarthropathy (DNOAP, Charcot joint or foot). Diabetic neuroosteoarthropathy is a destruction of the bone and joint of a non-infectious nature [1, 2, 3]. Diabetes, neuropathy, trauma and metabolic disorders of the bones lead to an acute localized inflammatory condition [4]. The inflammatory response causes structural changes in the bone tissue of the foot, which leads to abnormal plantar pressure, resulting in the formation of neurotrophic ulcers. From 10 to 72 % of diabetic foot ulcers are accompanied by osteomyelitis, what significantly increases the risk of lower limb amputation [5]. The prognosis for forefoot osteomyelitis is better than for midfoot and hindfoot osteomyelitis. In particular, the risk of amputation proximal to the level of the ankle joint is significantly higher for the hindfoot [6, 7]. Chronic osteomyelitis is a progressive inflammatory process that involves the bone and its surrounding tissues in one way or another, with periods of exacerbation and remission of various durations [8, 9].

Pathomorphological study is the "gold" standard for diagnosing osteomyelitis of the diabetic foot [10]. The HOES (histopathological osteomyelitis evaluation score) developed by A. Tiemann et al (2014) is a semi-quantitative histopathological assessment that improves the accuracy of differential diagnosis of acute and, especially, chronic osteomyelitis at different stages of the inflammatory process [11]. The HOES has proven its adequacy in clinical models of acute and chronic osteomyelitis of various locations [12, 13].

It is known that the presence of bone and cartilage fragments with inflammatory infiltrate in the hypertrophied synovial membrane is one of the pathohistological diagnostic criteria for DNOAP [5]. The development of an inflammatory process in the synovium is a trigger mechanism for joint destruction [14]. Molligan et al (2016) found that synoviocytes isolated from the synovial membrane of the Charcot joint are

more invasive and exhibit chondrolytic activity, which suggests the involvement of the synovial membrane in the pathogenesis of DNOAP [15]. To assess synovitis, Krenn et al (2017) developed a histopathological scale and a diagnostic algorithm to judge upon degenerative or post-traumatic synovitis (low-grade synovitis) and inflammatory-rheumatic disease (high-grade synovitis) with a sensitivity of 61.7 % and a specificity of 96.1 % [16]. The synovitis score according to Krenn et al (2006) has been widely used in various joint diseases, including arthroplasty [17].

Inflammation of the synovial membrane (synovitis) may result from trauma, bacterial and viral infections, wear and tear of the joints, allergic or neurogenic diseases [14]. In the Charcot joint, complicated by chronic osteomyelitis, there are traumatic, infectious, and neurogenic factors of synovitis [2]. The role of the synovial membrane in the pathogenesis of DNOAP remains poorly understood. Studies of the microscopic structure of the synovium of the Charcot joint are scarce and have been carried out with the participation of a small number of patients [15]. However, they are important for the development of therapeutic strategies in the treatment of this pathology.

Purpose To identify microscopic features and assess the severity of the inflammatory process in the synovial membrane of the Charcot joint in relation to the inflammatory phase of chronic osteomyelitis.

MATERIALS AND METHODS

The object of the study was fragments of the ankle joint (bone and cartilage blocks and synovial membrane) obtained during debridement of the osteomyelitis focus by sequesternecrectomy from 33 patients (13 women and 20 men, aged 29 to 80 years, median age 58 years [52÷60]) suffering from type 2 diabetes mellitus, distal polyneuropathy and a developed complication, diabetic neuroosteoarthropathy (chronic phase of Charcot's foot classified according to S. Eichenholtz: 8 patients in stage 2, 25 patients in stage 3) and chronic osteomyelitis. In the course of surgical debridement of the purulent focus, along with sequestrnecrectomy, the material was taken for pathomorphological study. Reduction and adaptation of the bones of the lower leg from the hindfoot, fixation of the segment with the Ilizarov apparatus, plasty of the skin defect, and installation of an active drainage system into the wound cavity were performed. The microbial landscape in all patients was gram-positive microflora of the genus *Staphylococcae* (85.8 %) as monoinfection, and in 14.2 % we observed strains from the genus *Proteae* (*Proteus Mirabilis*).

Inclusion criteria were the established diagnosis of diabetic neuroosteoarthropathy of the ankle joint, complicated by chronic osteomyelitis.

Exclusion criteria were diabetic neuroosteoarthropathy of the ankle joint, uncomplicated by osteomyelitis; other associated diseases or injuries that have a significant impact on the bone and joint structures.

The study followed the ethical standards set forth in the Declaration of Helsinki of the World Medical Association "Ethical principles for medical research involving human subjects" as amended in 2013 (minutes of the ethics committee of the institution No. 4 (68) dated 11/11/2020). Voluntary informed consent was obtained from all patients to publish the results of the study without disclosing their identity.

For histological study, bony- and cartilage blocks and fragments of the synovial membrane were fixed in neutral formalin; the samples were subjected to standard histological processing, and the bony- and cartilage blocks were preliminarily decalcified in a mixture of hydrochloric and formic acids. Paraffin sections were produced on a Richerd microtome (Austria), stained with hematoxylin and eosin, Masson's three-color method.

Part of the material (fragments of the synovial membrane) was cut into smaller pieces, fixed in a mixture of glutaric and paraformaldehyde in phosphate buffer with the addition of picric acid, and then additionally fixed in 1 % osmium oxide solution. Samples were embedded in epoxy resins; semi-thin sections, 0.5–1 μm thick, were produced on a Nova LKB ultratome (Sweden), stained with methylene blue and basic magenta. Histological preparations were studied and digitized on an AxioScope.A1 microscope with an AxioCam digital camera (Carl Zeiss MicroImaging GmbH, Germany) and Zen blue software (Carl Zeiss MicroImaging GmbH, Germany).

The phase of the inflammatory process of chronic osteomyelitis was assessed using the HOES semi-quantitative scale developed by A. Tiemann et al (2014), which includes an assessment of changes in bone, soft tissues and inflammatory infiltrate in points (0 – no changes, 1 – mild, 2 – moderate, 3 – severe). From each patient, 20 to 30 visual fields were analyzed. A score of $\geq$ 6 points corresponded to the acute inflammatory phase of chronic osteomyelitis, a score of $\geq$ 4 points corresponded to the subacute course of chronic osteomyelitis, and a score of < 4 points corresponded to the remission phase, a sluggish course of chronic osteomyelitis [11].

To determine the severity of synovitis, a semi-quantitative scale by V. Krenn et al was used (2006) [17]. It included an assessment of the thickness of the integumentary layer of the synovial membrane, cell density in the subsynovial layer, inflammatory infiltrate in points (no signs – 0, mild – 1 point, moderate – 2 points

and severe – 3 points). From each patient, 10 to 15 visual fields were analyzed. A score of 0–1 points means no synovitis, a score of 1 ≤ 4 points – mild synovitis, a score of 5 to 9 points corresponded to a high grade of synovitis. Semi-quantitative assessment of the inflammatory phase of chronic osteomyelitis and synovitis was carried out by three independent researchers.

Statistical data processing was carried out using the Attestat program (version 9.3.1, author I.P. Gaydyshev, Rospatent Certificate No. 2002611109) in Microsoft Excel spreadsheets. Quantitative characteristics are presented in the form of medians and quartiles (Me, Q1; Q3), since the hypothesis of normality was rejected, the correlation between the identified signs and the inflammatory phase was assessed using the nonparametric Spearman coefficient (r, power of the criterion 0.8–0, 9, 95 % confidence level. The degree of agreement between experts was determined by calculating the intraclass correlation coefficient (ICC, 95 % confidence level).

RESULTS

The light-optical study of bone and cartilage fragments in all cases revealed full-thickness articular cartilage defects, synovial pannus, foci of osteonecrosis in the subchondral zone, bone microsequesters, osteoclastic resorption of the subchondral bone plate, replacement of bone marrow structures with granulation and fibrous tissue, and the presence of an inflammatory infiltrate (Fig. 1). The severity of osteonecrosis, replacement of bone marrow structures with granulation tissue, the volume of the inflammatory infiltrate and its cell composition depended on the inflammatory stage of chronic osteomyelitis.

A semi-quantitative analysis revealed histological signs of the acute course of chronic osteomyelitis (pronounced osteonecrosis, numerous bone microsequesters, excessive osteoclastic resorption, replacement of the bone marrow with granulation tissue, cell composition of the inflammatory infiltrate: lymphocytes, plasma cells, neutrophils more than five in 11 patients (A. Tiemann et al (2014) [11] score was from 7 to 9 points). Histological signs of a subacute course of chronic osteomyelitis (moderate osteonecrosis, replacement of the bone marrow with granulation tissue, cell composition of the inflammatory infiltrate represented by lymphocytes, plasma cells, macrophages, neutrophils less than 5) were detected in 16 patients (A. Tiemann et al (2014) [11] score of 4–5). Signs of sluggish chronic osteomyelitis in remission (osteonecrosis of low severity, areas of bone marrow fibrosis are few, fatty bone marrow predominated, the cell composition of the inflammatory infiltrate represented by histiocytes, lymphocytes, plasma cells) in 6 patients (A. Tiemann et al (2014) [11] score was 3 points). The average value of the intraclass correlation coefficient (ICC) of three experts was 0.95 [0.92–0.97].

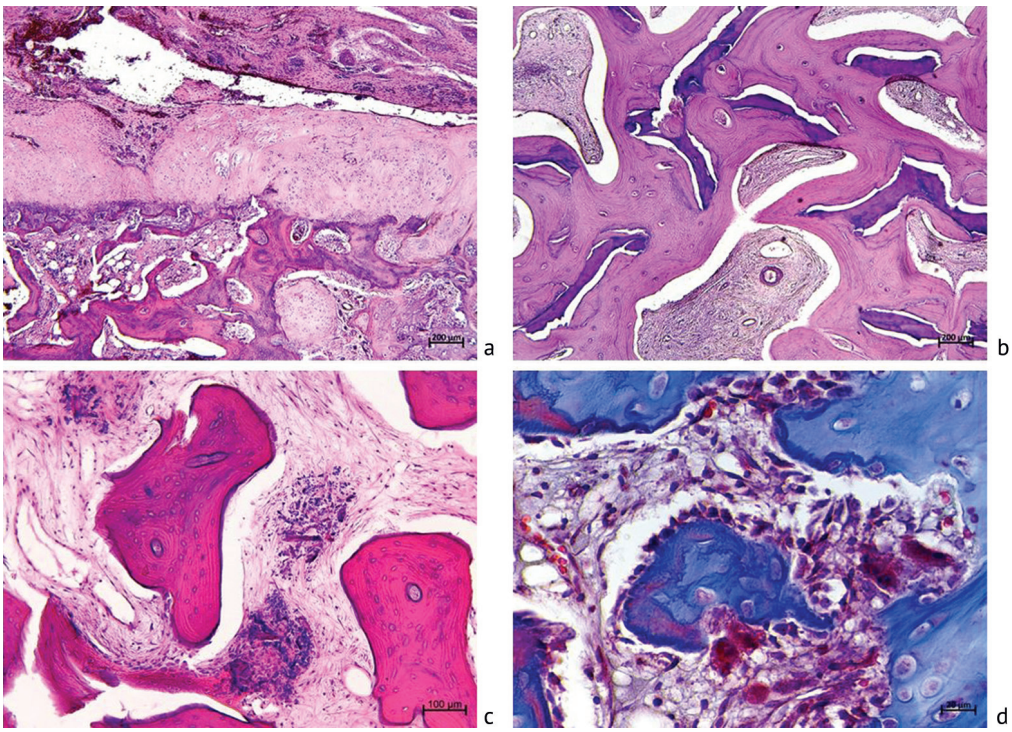

Fig. 1 Osteo-cartilaginous fragments of the Charcot ankle complicated by chronic osteomyelitis: a synovial pannus, resorbing articular cartilage, osteonecrosis foci in the subchondral zone, partial resorption of the subchondral bone plate; b pronounced osteonecrosis in the subchondral zone, bone marrow replacement with granulation tissue; c multiple bone microsequesters; d on the surface of the trabecula, active osteoblasts on one side and osteoclasts resorbing bone tissue on the other side, penetration of the bone marrow pannus into the deep zone of the cartilage. Paraffin sections, stained with hematoxylin and eosin (a, b, c), Masson's three-color method (d). Magnification ×40 (a, b), ×100 (c), ×400 (d)

Microscopic examination of fragments of the joint capsule revealed hyperplasia of the synovial membrane in all cases (Fig. 2 a). There were fragments of cartilage and bone trabeculae surrounded by cell infiltrate and giant multinucleated cells of the foreign body type (Fig. 2 a, b).

The assessment of synovitis by V. Krenn et al (2006) [17] showed that 15 patients had mild synovitis and 18 patients had high-grade synovitis. The mean ICC of three experts was 0.92 [0.90–0.94].

The statistical analysis revealed a high (from 0.7 to 0.9 on the Chaddock scale) positive correlation relationship between the severity of the inflammatory phase of chronic osteomyelitis and synovitis (Spearman correlation coefficient r = 0.76, p = 1.7E-16).

In patients with sluggish chronic osteomyelitis, the synovitis score ranged from 3 to 4 points [median 4; 25–75 %; 3–4]. In patients with signs of a subacute course of chronic osteomyelitis, the score for synovitis was from 4 to 5 points [median 4; 25–75 %; 4–5]. In patients with signs of an acute course of chronic osteomyelitis, the score of synovitis was from 5 to 8 points [median 7; 25–75 %; 5–7].

In the samples of the synovial membrane of patients with sluggish chronic osteomyelitis, extensive areas with destruction of the integumentary layer and replacement with fibrous tissue were detected. Synovial villi were not expressed; in the integumentary layer, synoviocytes were located in 1–2 layers or were completely absent (Fig. 2 c). The subsynovial layer was characterized by moderately increased cellularity, microvessels with signs of perivascular edema and plethora. The inflammatory infiltrate was diffusely located, predominantly perivascularly; the cell composition were lymphocytes, histiocytes, and plasma cells.

In the samples of the synovial membrane of patients with active chronic osteomyelitis (subacute stage and acute stage), thickening of the integumentary layer of the synovial membrane was noted due to an increase in the number of layers of synoviocytes (from six or more) and the presence of compacted foci of inflammatory infiltrate (Fig. 2 d). In the integumentary and upper subsynovial layer, there was a high number of vessels of the microvasculature. In most vessels, a pronounced increase in wall thickness was revealed both due to hyperplasia of endotheliocytes and due to hyperplasia of the media components, which caused narrowing of the lumens or their complete closure (Fig. 2 e). Cellularity was significantly increased; an inflammatory infiltrate with a high content of plasma cells (Fig. 2 e) and neutrophils (Fig. 2 f) was detected. In the subsynovial layer, most of the vessels were filled with erythrocytes; fields with accumulation of hemosiderin granules located near the vessels were observed (Fig. 2 e); and blood cells outside the vascular wall (Fig. 2 f).

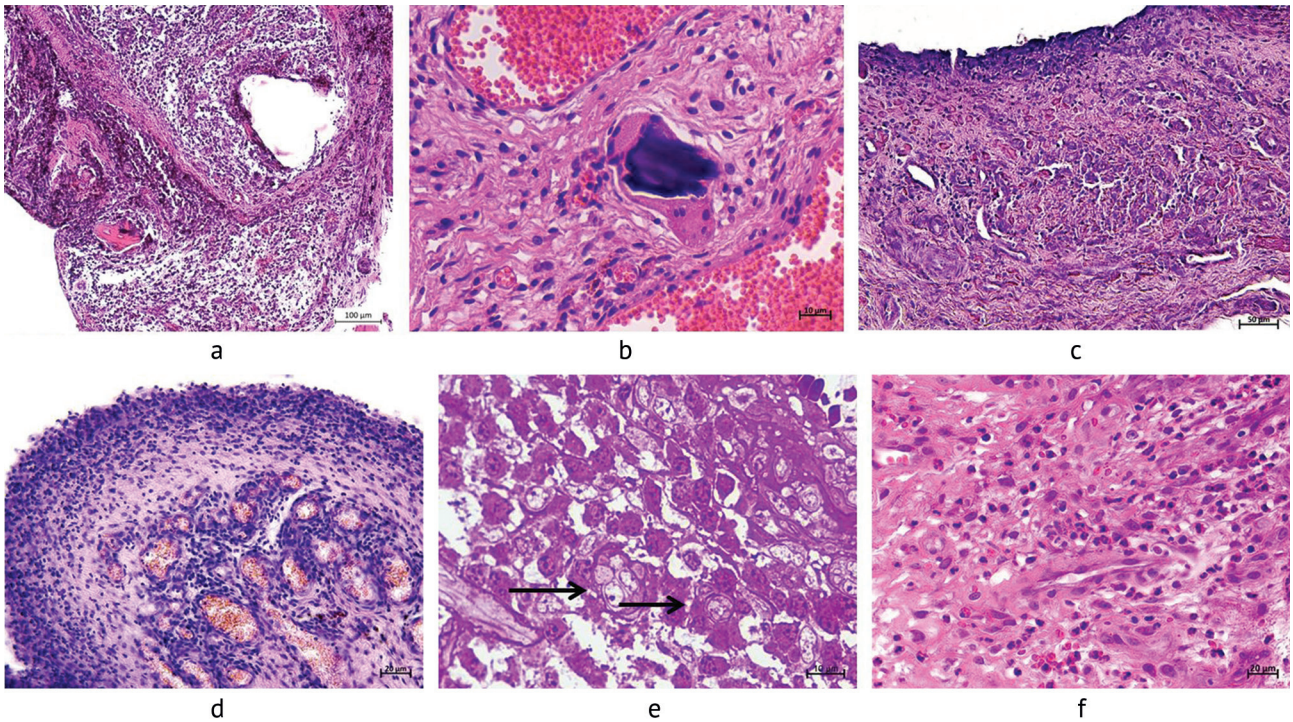

Fig. 2 Synovial membrane of Charcot ankle joint complicated by chronic osteomyelitis. A fragment of a bone trabecula in a hyperplastic synovial membrane with an inflammatory infiltrate (a) and a giant multinucleated cell of the foreign body type absorbing a fragment of a bone trabecula (b) in subacute chronic osteomyelitis. Focal fibrosis of the integumentary layer, synovial villi are not expressed, hypervascularization of the subsynovial layer (c) in sluggish chronic osteomyelitis. Villous hyperplasia, increased vascularization, hyperemia, hemosiderin in the subsynovial layer (d), microvessels with closed lumen (arrows), compacted inflammatory infiltrate with a high content of plasma cells (e) and neutrophils, erythrocytes outside the vascular wall (f) in acute chronic osteomyelitis. Paraffin sections, stained with hematoxylin and eosin (a, b, c, d, f), semi-thin section, stained with methylene blue and basic fuchsin (e). Magnification ×125 (a), ×600 (b), ×200 (c), ×400 (d), ×1000 (e), ×500 (f)

DISCUSSION

The pathogenesis of Charcot osteoarthropathy is still the subject of discussion. The factors of genetic predisposition, inflammation, changes in the peripheral nervous system, and bone metabolism disorders involved in the development of this disease are the subject of current research [18, 19].

The synovial membrane certainly plays an important role in maintaining the normal structure of the articular cartilage [20]. In the condition of synovitis, the synovial membrane is the driving force behind the destruction of the articular cartilage in a number of diseases such as rheumatoid, psoriatic, juvenile and idiopathic types of arthritis, lupus, gout, and Lyme disease [1, 14].

In our study, the presence of bone and cartilage fragments deep inside the synovial membrane of the joints in diabetic neuroosteoarthropathy complicated by chronic osteomyelitis allowed us to differentiate it from osteoarthritis [21]. Synovitis was revealed in all our patients, in 45 % of cases it was mild and in 55 % of cases it was pronounced.

Regardless of the inflammatory phase of chronic osteomyelitis, in all the cases studied, hyperplasia, hypervascularization and hyperemia of the synovial membrane with the presence of bone and cartilage fragments, inflammatory infiltrate, synovial pannus, invading articular cartilage, were observed. From the side of the vessels, a pronounced narrowing of the lumens or their complete closure was seen both due to hyperplasia of endotheliocytes and due to hyperplasia of media components. The changes in the vessels of the microvasculature of the synovial membrane indicated a disorder of microcirculation, the development of inflammatory processes, which is prognostically unfavorable for the restoration of joint function.

It is known that tissue hypoxia activates the expression of proangiogenic factors, including vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGF) [22].

The resulting hypervascularization of the synovium promotes inflammatory infiltration, which creates a vicious circle of uncontrolled inflammatory responses. The inflammatory products emanating from the synovial pannus, growth factors, cytokines, and metalloproteinases destroy the adjacent articular cartilage matrix and increase osteoclastic activity in the subchondral zone [14, 23].

Inflammation and increased activity of osteoclasts are well recognized factors in the rapid bone loss seen in Charcot foot, although the relationship between the two is not fully understood [15, 24, 25, 26]. Molligan et al (2016) in a study of seven patients with Charcot osteoarthropathy reported hypertrophy, increased vascularization and inflammatory infiltration of the synovium, distribution of cartilage and bone fragments in the synovium, increased expression of inflammatory cytokines and metalloproteinases involved in the maturation and proliferation of osteoclasts and bone tissue remodeling. The authors conclude that B-synoviocytes or fibroblast cells play an important role in joint destruction in diabetic neuroosteoarthropathy [15].

Osteomyelitis exacerbates bone loss, since a number of factors are known to trigger a cascade of biochemical reactions, resulting in the formation of pro-inflammatory cytokines, local release of nitric oxide, poor blood supply, what leads to the death of osteoblasts, enhanced osteoclastogenesis, and increased bone resorption [27, 28, 29, 30].

In our study, in all the cases, full-thickness articular cartilage defects, osteoclastic resorption of the subchondral bone plate, disruption of the chondrohematic barrier, and penetration of blood vessels into the cartilage from the side of the subchondral bone were recorded. Assessment of the stages of chronic osteomyelitis according to the HOES system showed that 82 % of cases were characterized by its subacute and acute course. According to the statistical data, the severity of synovitis positively correlated with the inflammatory phase of chronic osteomyelitis; the Spearman correlation coefficient of 0.76 indicated a highly close relationship.

The average values of the intraclass correlation coefficient of three experts were 0.95 [0.92–0.97] and 0.92 [0.90–0.94]; they indicated excellent reliability of the systems of Tiemann et al (2014) [10] and Krenn et al (2006) [17].

In patients with sluggish chronic osteomyelitis, the score of Krenn et al (2006) [17] indicated mild synovitis. In patients with signs of subacute chronic osteomyelitis, synovitis of varying severity was recorded, from mild to severe. In patients with signs of acute chronic osteomyelitis, a high grade synovitis was noted. In sluggish chronic osteomyelitis, synovial villi were not expressed, but focal fibrosis of the integumentary layer, infiltration by lymphocytes, histiocytes, and plasma cells were observed. In the active inflammatory phase (acute and subacute course) of chronic osteomyelitis, villous hyperplasia prevailed, the formation of villi due to the proliferation of synoviocytes of the integumentary layer; hemosiderin, plasma cells, lymphocytes, macrophages, and neutrophils were determined.

CONCLUSION

In diabetic osteoarthropathy of the ankle joint complicated by chronic osteomyelitis, irreversible structural changes in the synovial membrane contribute to the formation of synovial pannus and the progression of destruction of the articular cartilage and subchondral bone. The severity of synovitis positively correlates with the inflammatory phase of chronic osteomyelitis.

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