VERTEBRAL FORM OF NON-BACTERIAL OSTEOMYELITIS: CLINICAL AND LABORATORY FEATURES AND TREATMENT CHARACTERISTICS

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Objective. To study clinical and laboratory features of spinal lesions associated with non-bacterial osteomyelitis (NBO), to define the role of surgery in its diagnosis and treatment, and to analyze the efficacy of different treatment regimens.
Material and Methods. Retrospective two-center cohort of 54 children with NBO, including 18 patients with vertebral lesions was studied. The level of evidence is 3.
Results. Vertebral form of the non-bacterial osteomyelitis is characterized by high frequency of multifocal bone lesions. The features of clinical and X-ray manifestations of the vertebral form of NBO, its diagnosis and medical treatment are presented. First of all NBO should be differentiated from infectious (tuberculosis) and neoplastic lesions of the skeleton. Non-steroid anti-inflammatory drugs are not effective for the relief of pain in the NBO vertebral form, preference should be given to bisphosphonates and TNF-a inhibitors. Indications and volume of surgical techniques for diagnosis and treatment of this pathology are specified.
Conclusion. Management of patients with the vertebral form of NBO should be interdisciplinary and carried out with the assistance of doctors of various specialties – pediatricians, rheumatologists, orthopedists, surgeons, phthisiatrician, etc.
Key Words: non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, spine, treatment, bisphosphonates, TNF-inhibitors, treatment.

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The non-bacterial osteomyelitis (NBO) is a rare non-infectious autoinflammatory disease of the skeleton, occurring primarily in children and adolescents. It is characterized by an unpredictable natural course associated with both multiple relapses and the possibility of spontaneous remission [10]. The pathogenesis of NBO is relatively well studied. It is caused by an imbalance between pro- and anti-inflammatory cytokines, namely by a decrease in the production of interleukin-10 (IL-10) by monocytes and an increase in a tumor necrosis factor-α inhibitor (iTNF-α) [12, 13].

In the domestic medical literature, the orthopedic aspects of NBO were sufficiently well systematized by A.P. Berezhnoy and A.A. Ochkurenko [2, 5] and in individual clinical observations [1]. These studies were based on the contemporary data and did not focus on vertebral lesions. In a review article intended primarily for pediatricians and rheumatologists [3], we attempted to present a joint approach of surgeons and physicians to the problem. However, spine pathology experts have still remain outside the scope of these discussions despite the fact that involvement of the vertebrae in the pathological process is one of the quite frequent disease localizations, the presence of which significantly affects an interpretation of disease, choice of diagnostic methods, tactics of therapeutic and surgical solutions, and prognosis of outcomes [9, 11].

A very limited number of international studies and the lack of domestic publications devoted to NBO-associated spinal lesions prompted us to present our own experience of joint work of pediatric rheumatologists and spinal surgeons and compare the experence with the literature data.

The objective of our work was to study clinical and laboratory features of spinal lesions associated with non-bacterial osteomyelitis, define the role of

surgery in the diagnosis and treatment of NBO, and analyze the efficacy of different treatment regimens.

Material and Methods

A retrospective, observational, two-center study was conducted in the Pediatric Department of the Clinics at the Saint-Petersburg State Pediatric Medical University (SPbSPMU) dedicated to the diagnosis and treatment of rheumatoid and systemic non-neoplastic diseases in children and the Pediatric Surgery and Orthopedics Clinic of the Saint-Petersburg Research Institute of Phthisiopulmonology (SPbRIP) focused on the surgical treatment of children with destructive bone lesions. The primary cohort of NBO patients was formed based on common databases in accordance with the following inclusion criteria:

– age under 18 years;

– the patient's primary admission to any of the mentioned clinics in the period from January 01, 2009 to December 31, 2015;

– detection of bone pathology meeting the criteria used to diagnose "non-bacterial osteomyelitis" or "chronic multifocal recurrent osteomyelitis" [15] (Table 1).

According to the classical criteria by Jansson et al. [15], the NBO diagnosis can be made on the basis of two major criteria or one major and three minor criteria. In our study, we considered it obligatory for patients to have two (first and fourth) major Jansson's criteria and at least one minor criterion to be included in the cohort. In the presence of multiple bone lesions, a study of material from the most symptomatic lesion was obligatory. According to the fourth Jansson's criterion, a bacteriological study of material was a must.

Patients were automatically excluded from the NBO database if the following characteristics were identified:

1) positive results of analyses for specific or nonspecific microbiota;

2) positive results of any modern bacteriological analysis, such as PCR, molecular genetic testing, etc. for any microbiota;

3) a biopsy picture of caseous-necrotic inflammation (typical of tuberculosis infection as the most frequent variant of specific granulomatous osteomyelitis) or morphological changes indicative of tumor diseases.

The presence of the bone's destructive process was confirmed by radiographic techniques (X-ray, CT, and/or MRI); patients older than 5 years of age underwent radionuclide imaging of the skeleton with Tc-99.

Before treatment, all patients underwent clinical and laboratory tests including hemoglobin concentration, leukocyte and platelet counts, the erythrocyte sedimentation rate, and the C-reactive protein level. Material for bacteriological and histological studies was sampled either from a closed bone biopsy or from surgery.

At the second stage, 18 patients with spinal cord lesions were selected from an overall cohort of 52 NBO patients with the age of disease onset ranging from 8 months to 15 years. Therefore, a group of patients with the so-called "vertebral form of NBO" was formed, and 34 patients without spinal lesions comprised a group with the peripheral form of NBO.

The study flow chart is shown in Fig. 1.

The patients' condition, including activity of the process and pain severity, was subjectively evaluated by using a 100-point visual analogue scale (VAS), with 0 and 100 indicating the lowest and highest values of an indicator, respectively. Family history of autoimmune diseases, concomitant rheumatic diseases, and clinical features were studied in all patients.

In accordance with the modern data, patients with the established NBO diagnosis underwent the so-called sequential therapy accounting for the distribution and severity of the disease [10]. All drugs were grouped into 5 classes (steps): 1) nonsteroidal anti-inflammatory drugs (NSAIDs) were used as first-line therapy in patients with the peripheral form; 2) methotrexate and 3) sulfasalazine were more often used in patients with comorbid immunopathological diseases; 4) bisphosphonates were used primarily for the vertebral form as well as for the peripheral form if previous therapy

Table 1
Diagnostic criteria of non-bacterial osteomyelitis [15]

Major criteria	Minor criteria
1. Local changes in a bone: bone loss, destruction, osteolysis or osteosclerosis, and periostitis identified during radiographic or CT studies. 2. Multifocal skeletal lesions. 3. Palmoplantar pustulosis and psoriasis. 4. Negative results of blood and bone biopsy cultures.	1. The general state of health is slightly affected. 2. Normal blood count indicators or minor changes in CRP and ESR. 3. Disease duration longer than 6 months. 4. Hyperostosis. 5. Associated autoimmune diseases, apart from palmoplantar pustulosis and psoriasis. 6. Positive family history of autoimmune diseases, auto-inflammatory diseases, or chronic non-bacterial osteomyelitis.

failed; 5) genetically engineered drugs, namely TNF-α inhibitors (iTNF-α).

In the case of combination therapy, an administered drug was referred to the highest class (step) during analysis of the efficacy of treatment.

The efficacy of treatment was analyzed using VAS and objective criteria, including the absence of disease recurrences and a reduction in the disease activity based on the laboratory indicators CRP and ESR.

We used Statistica 6.0 Biostat and Microsoft Excel software in statistical analysis, applying methods of descriptive statistics (median Me and interquartile range 25–75 %) for analysis of quantitative variables, χ^2 tests and the Fischer exact test for comparison of two groups of categorical variables, and the Mann-Whitney test for comparison of quantitative variables.

Results

A comparison of the vertebral and peripheral NBO groups revealed no significant differences by gender, positivity of family history, and the presence of rheumatoid and/or immunopathological comorbid disease. Vertebral lesions presented as a monofocal form only in 2 (11.1 %) patients; 16 (88.9%) patients presented with a typical multifocal process with axial and peripheral skeleton lesions.

Table 2 presents the characteristics of patients with vertebral NBO. It is obvious that, first, the spinal lesion has primarily a multi-level nature; second, the rate of thoracic vertebral lesions significantly predominates over that of cervical and, especially, lumbar lesions.

A detailed analysis of the features of skeletal extravertebral lesions was not an objective of this article and was provided in other publications [3, 4]. It was statistically proven (Table 3) that the number of pathological bone lesions associated with vertebral NBO doubled, on average, that associated with peripheral NBO; also, the process significantly more frequently involved other bones conditionally attributed to the central or axial skeleton: the pelvic bones ($p = 0.08$) and sternum ($p = 0.04$), with the foot bones being affected more rarely ($p = 0.006$).

There were no significant differences between the groups in the level of hemoglobin, leukocytes, and platelets as well as in the febrile temperature frequency at the disease onset. At higher CRP levels, the significance of differences in patients with vertebral NBO was not proven.

Efficacy of treatment. Out of 52 patients, 18 (34.6 %) including 4 patients with the vertebral form and 14 with the peripheral form received NSAIDs as first line therapy. In the total cohort of NBO patients, remission was achieved in 52.6 % of patients receiving NSAIDs. While there was a significant decrease in the indicators reflecting the treatment efficacy in peripheral NBO, there were no similar results in the case of vertebral NBO (Fig. 2). Noteworthy, a doctor, a patient, and parents of children evaluated the efficacy of NSAIDs almost identically.

In children receiving bisphosphonates (pamidronic acid-based medications), a marked reduction in the pain intensity (VAS) was observed for both vertebral ($p < 0.01$) and peripheral ($p < 0.005$) forms of the disease (Fig. 3). It should be noted that pamidronic acid was administered to patients with severe pain, whose median baseline VAS score (assessed by parents and physicians) was more than 70.

Nine (17.3 %) patients (3 and 6 patients with vertebral and peripheral NBO, respectively) received therapy with TNF-α inhibitors (etanercept, adalimumab, infliximab). Therapy with iTNF-α was effective in both groups, but its efficacy was statistically proven only in the case of the peripheral form (Fig. 4).

In a total cohort of NBO patients receiving pamidronic acid, remission was achieved in 88.8 % of patients. In a total cohort of NBO patients receiving iTNF-α, remission was achieved in 73.3 % of patients. As mentioned, prescription of methotrexate and sulfasalazine was associated with the presence of concomitant rheumatoid diseases and was effective in 44.4 % and 57.1 % of patients receiving methotrexate and sulfasalazine, respectively.

Antibacterial therapy, which was usually used during disease diagnosis, did not improve the clinical and laboratory indicators.

Spinal surgery was indicated for 5 patients: in 4 cases, surgery was carried out due to non-informative results of the

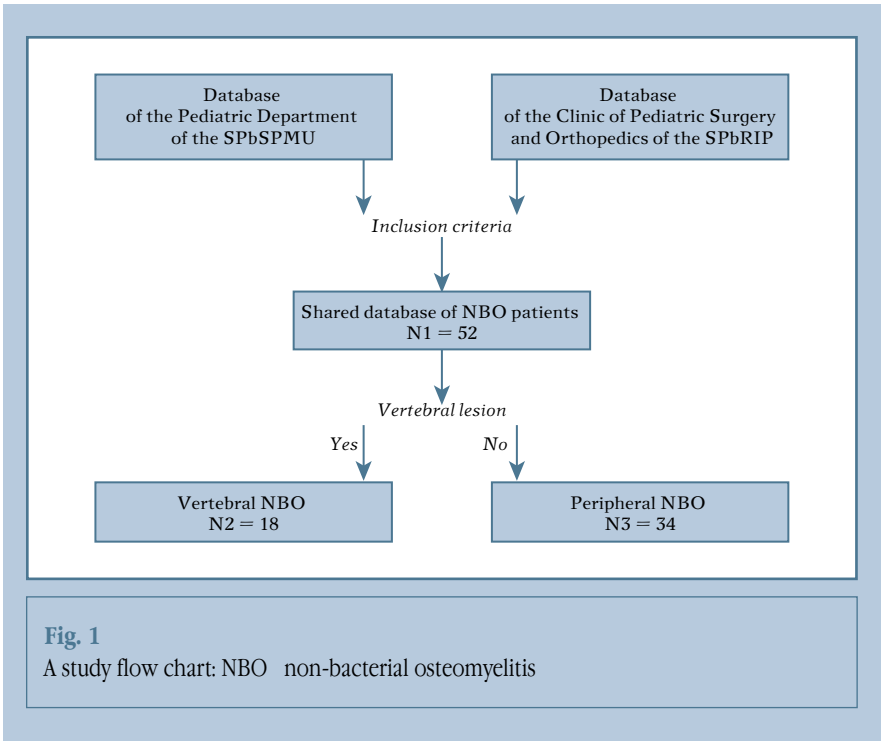

Fig. 1
A study flow chart: NBO non-bacterial osteomyelitis

closed biopsy or severe spinal instability manifested as pain provoked by movements and intractable to an orthosis. In one case, reconstruction of the cervical spine was performed because of the development of spinal deformity associated with a C5 lesion during NBO treatment. If a combination of conservative treatment and surgery was necessary, the decision on the time, tactics, and action sequences was made collectively. The tactics and amount of surgery were determined by surgeons.

Clinical case 1. A 15-year-old female patient B. was sick for 8 months. She underwent an examination due to long-term pain in the chest and spine. CT and

Table 2
Characteristics of children with vertebral non-bacterial osteomyelitis after treatment

Patient	Gender	Age of onset, years	Affected level		Associated rheumatic disease (immune disease)	Treatment
			vertebrae	extravertebral		
1	F	5	T1	–	Arthritis associated with Crohn's disease	Mesalazine, pamidronic acid, infliximab
2	F	4	C6, T1–T4	Clavicle, sternum, rib		Pamidronic acid, NSAIDs
3	M	15	C3–C5, T1	–	Enthesitis-related arthritis	NSAIDs, pamidronic acid, sulfasalazine, surgery
4	M	5	T4, T10	Sternum, pelvic bones	Juvenile idiopathic arthritis	NSAIDs, methotrexate, pamidronic acid
5	M	7	C2–C6	Clavicle, pelvic bones	Juvenile idiopathic arthritis	NSAIDs
6	M	6	C1, T1–T12, L1–L5	–	Juvenile ankylosing spondylitis	Pamidronic acid, NSAIDs
7	F	10	L4–L5	Foot bones, tibia, rib	Juvenile idiopathic arthritis	Pamidronic acid, NSAIDs
8	F	11	C1–C5, T7, T11	–	–	Pamidronic acid, NSAIDs
9	M	1	S1	–	Juvenile idiopathic arthritis, uveitis	NSAIDs, methotrexate, TNF-inhibitors
10	F	7	T6, T12	–	–	–
11	F	7	T12	Tibia	–	–
12	M	9	T7	Fibula	Juvenile idiopathic arthritis	–
13	M	13	S1	Femur	Juvenile idiopathic arthritis	NSAIDs, glucocorticosteroids, sulfasalazine
14	M	12	C3–C4, C6–C7	Pelvic bones	–	NSAIDs, pamidronic acid, glucocorticosteroids
15	M	8	T8	Femur, tibia	–	Surgery
16	F	8	T6	Radial bone	–	NSAIDs, glucocorticosteroids, surgery
17	F	2	L3	Foot bones	–	NSAIDs, surgery
18	M	1	T1, T2, T7–T9	Femur	–	NSAIDs, surgery

Table 3
Comparative characteristics of patients with vertebral and peripheral non-bacterial osteomyelitis (NBO)

Indicator	Vertebral form (n = 18)	Peripheral form (n = 34)	p
Gender, girls, n (%)	7 (38.9)	18 (52.9)	0.33
Age of onset, years	8,2 (5.9; 10.9)	8,7 (4.3; 11.2)	0.86
Positive family history of rheumatic diseases, n (%)	2 (11.1)	2 (5.9)	0.6*
Associated rheumatic diseases, n (%)	11 (61.1)	24 (70.6)	0.49
Monofocal forms, n (%)	2 (11.1)	8 (23.5)	0.46*
Skeletal lesions, n (%):			
– femur	7 (38.9)	11 (32.4)	0.64
– tibia	6 (33.3)	17 (50.0)	0.25
– fibula	2 (11.1)	7 (20.6)	0.47*
– foot bones	3 (16.7)	19 (55.9)	0.006
– pelvic bones	7 (38.9)	5 (14.7)	0.08*
– clavicle	3 (16.7)	3 (8.8)	0.4
– sternum	4 (22.2)	1 (2.9)	0.04*
– humerus	1 (5.6)	3 (16.7)	1.0*
– ribs	3 (16.7)	1 (2.9)	0.11
– radial bone	1 (5.6)	2 (5.9)	1.0*
– ulnar bone	0 (0.0)	2 (5.9)	0.54*
– hand	0 (0.0)	0 (0.0)	–
– upper jaw	0 (0.0)	1 (2.9)	1.0*
– scapula	1 (5.6)	0 (0.0)	0.35*
Febrile seizure at disease onset, n (%)	7 (38.9)	13 (38.2)	0.96
Mean number of foci in a patient	6,0 (2.0; 9.0)	3,0 (1.0; 4.0)	0.01
Hemoglobin, g/L	111 (100; 126)	121 (110; 129)	0.19
Leukocytes, x 10^9/L	8,3 (6.7; 9.2)	7,8 (6.6; 9.0)	0.66
Platelets, x 10^9/L	284 (262; 386)	336,5 (271; 426)	0.34
ESR	30,0 (13.5; 43.0)	24,0 (11.0; 40.0)	0.81
CRP, mg/L	27,9 (4.3; 34.0)	7,6 (3.6; 33.2)	0.43
Clinical evaluation of NBO activity on VAS, mm:			
– overall assessment by the patient/by the parent	45 (38; 65)	52 (35; 67)	0.92
– assessment of pain by the patient/by the parent	44 (34; 78)	45 (27; 75)	0.68
– medical assessment	45 (37; 85)	57 (34; 70)	0.61
Diagnostic pause, months	8,1 (3.3; 12.0)	6,1 (1.7; 18.6)	0.7

*Fisher exact test.

MRI scans (Fig. 5) revealed destructive changes in the sternal body and a T8 vertebral body hemangioma. At the place of residence, the patient underwent tuberculosis chemotherapy due to suspected sternum tuberculosis, after which the pain persisted. A bone scan (December 2015) revealed hyperfixation of a radiotracer (RT) in the sternal body (147 %) and moderate RT uptake in the projection of the posterior portion of the T8 body with extension to the rib head on the left (110 %). At admission to the Clinic of Pediatric Surgery and Orthopedics of the SPbRIP (29.12.2015), the patient presented with moderate sternal pain, a normal general state, and normal temperature. Clinically, there was dense tissue edema in the sternum area, without hyperemia, and painless on palpation. Peripheral lymph nodes were non-enlarged, mobile, and painless. There was no pathology of the cardiovascular and respiratory systems and abdominal organs. A complete blood count revealed no changes, except for an increased ESR of 21 mm/h: (hemoglobin: 119 g/L, erythrocytes: 3.8 x 1012/L, leukocytes: 5.9 x 109/L; band cells: 2 %, segmented cells: 63 %, lymphocytes: 27 %, monocytes: 3 %).

12.01.2016, the patient underwent necrectomy of the 1–3 sternal segments and reconstruction with an autologous bone graft. The results of bacteriological (bacterioscopic, culture, and molecular genetic) tests of surgery material for specific and non-specific microflora were negative. A histological examination of surgical specimens revealed a morphological picture of chronic osteitis with minimal activity.

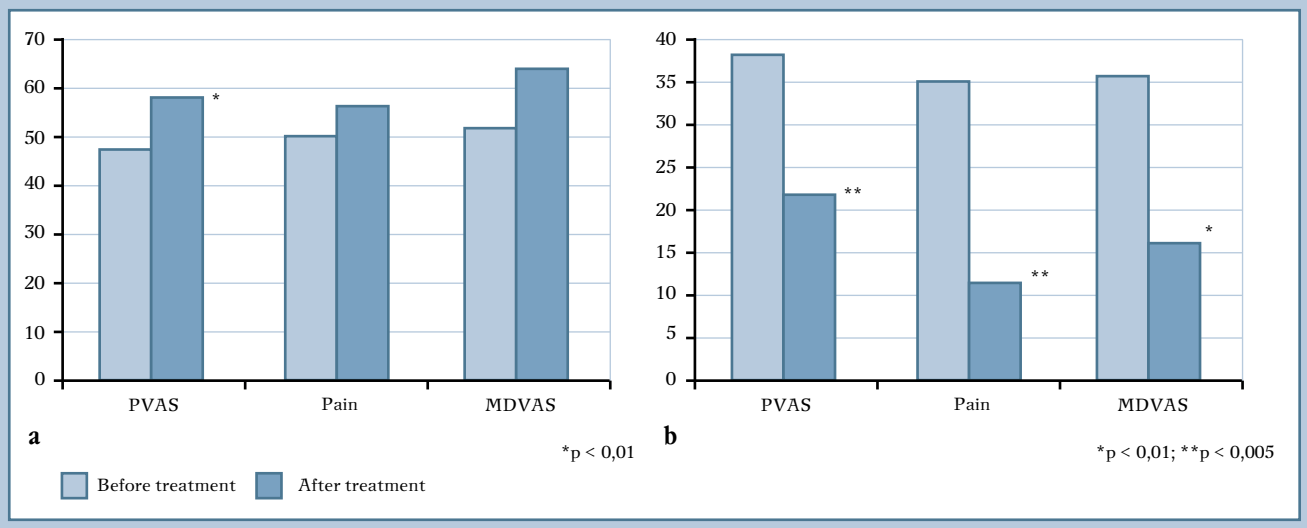

Fig. 2
Evaluation of the NSAID efficacy in treatment of patients with vertebral **(a)** and peripheral **(b)** forms of non-bacterial osteomyelitis: PVAS – assessment of well-being (VAS) made by the patient's parents; pain – pain intensity; MDVAS – assessment of well-being (VAS) made by the attending doctor

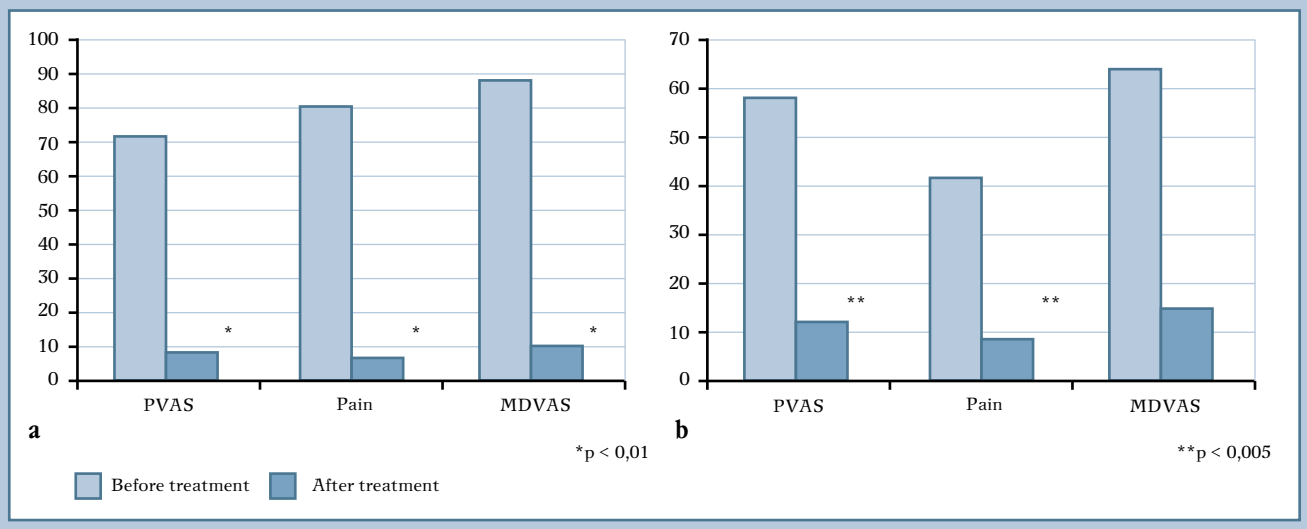

Fig. 3
Evaluation of the pamidronic acid efficacy in treatment of patients with vertebral **(a)** and non-vertebral **(b)** forms of non-bacterial osteomyelitis: PVAS – assessment of well-being (VAS) made by the patient's parents; pain – pain intensity; MDVAS – assessment of well-being (VAS) made by the attending doctor

During the stay at the hospital, the girl began to complain of pain in the spine and hip joints. MRI scans revealed bone marrow edema in the anterosuperior portions of the L3 body as well as degenerative changes in the L4–L5 (decreased hydrophilicity) and L5–S1 discs (decreased hydrophilicity and height). CT scans (Fig. 5) revealed small destructive lesions, up to 3 mm in diameter, with perifocal sclerosis in the area of the superior subchondral plate of the L3 vertebra and inferior plate of the L4 vertebra. The L5–S1 disc was uniformly reduced, without reactive changes in the contacting bone portions.

The patient consulted with a rheumatologist. Given the presence of multifocal lesions with the verified inflammatory non-infectious focus in the sternum, involvement of the spine, and a provi-

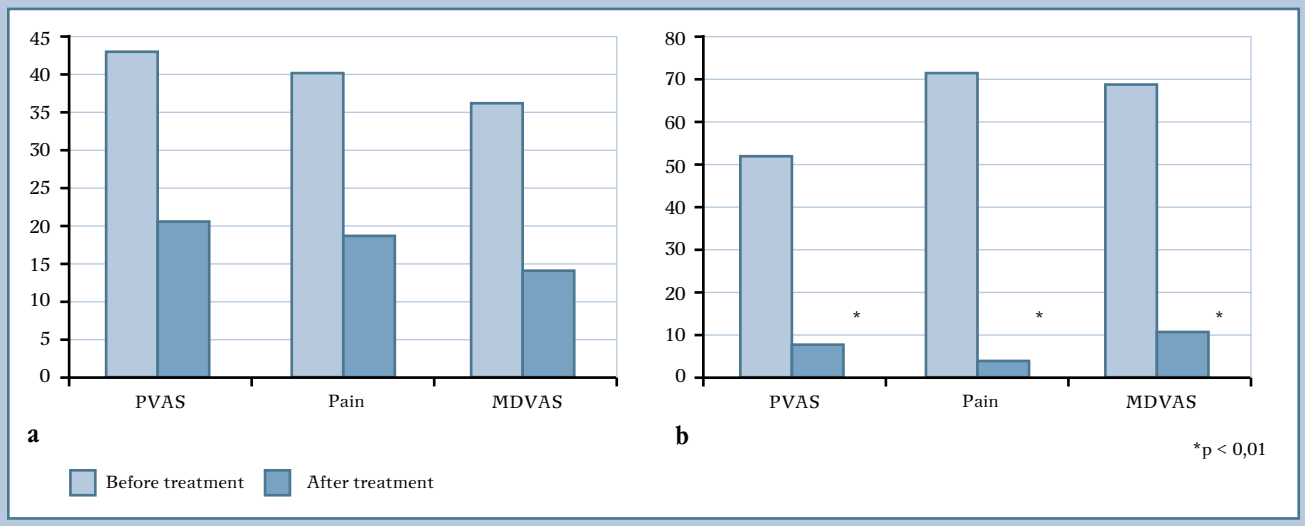

Fig. 4
Evaluation of the efficacy of TNF-α inhibitors in treatment of patients with vertebral **(a)** and non-vertebral **(b)** forms of non-bacterial osteomyelitis: PVAS – assessment of well-being (VAS) made by the patient's parents; pain – pain intensity; MDVAS – assessment of well-being (VAS) made by the attending doctor

sional diagnosis of chronic multifocal osteomyelitis, the patient was treated with indomethacin at a dose of 2 mg/kg/day and pamidronic acid at a dose of 1 mg/kg/day for 3 days on a quarterly basis. The treatment led to relief of the pain and normalization of the ESR. The child has continued treatment and has been under follow-up.

Clinical case 2. A 10-year-old female patient R. was sick for the past 2 months. The patient complained of aggravated back pain after chest injury. Plain radiography revealed a reduced height of the T7 vertebra. On the basis of the CT and MRI data, the changes were assessed as a pathological fracture accompanied by a bilateral paravertebral soft tissue component (Fig. 6). Radioisotope scanning detected radiotracer uptake of up to 150 % in the T6–T7 area without other RT uptake localizations. The patient was hospitalized to the Clinic of Pediatric Surgery and Orthopedics of the SPbRIP with pain scored 7 (VAS) and ESR of 42 mm/h. The patient was neurologically intact. The differential set included first of all neoplastic disease (histiocytosis from Langerhans cells) and tuberculous spondylitis. The patient underwent a targeted closed percutaneous punch biopsy of the vertebral body, the result of which was regarded as uninformative (specimens were described as chronic inflammation elements lacking specific features). The patient was recommended for a resection biopsy for treatment and diagnostic purposes. The child underwent resection of the T7 body and anterior fusion using titanium mesh with an autologous bone. An analysis of material for nonspecific and specific microflora was sterile; the results of molecular genetic tests for microbiota were negative. A histological study identified chronic inflammation with leukocyte infiltration without specific necrosis and neoplastic transformation. The results of immunohistochemical tests for tumor markers and rare infections were negative. The patient's condition was assessed as a monostotic vertebral form of non-bacterial osteomyelitis. The child consulted with a rheumatologist and received pamidronate therapy that provided a positive clinical effect. The patient has been monitored distantly. The relapse-free period at the time of analysis was 4 months; the ESR decreased to 14 mm/h.

Clinical case 3. An 8-year-old female patient B. At the age of 4 years, the child, being in a healthy condition, developed an acute torticollis episode; despite periodic complaints of pain and restricted motion in the cervical spine, there was no treatment. At the age of 5 years, a painful bone lesion developed in the sternal end of the left clavicle. At the place of residence, the patient underwent a bone marrow puncture and a clavicle biopsy that revealed no cancer and specific osteomyelitis signs; nonspecific inflammation was identified; the bacterial culture test was negative. Total body MRI revealed bone marrow edema foci in the left clavicle, right 3rd rib, C6 and T1–T4 vertebrae, and sternum. Later, pain developed in the middle third of the left tibia. The patient underwent the first examination at a rheumatology department at the age of 6 years (January 2013). The condition, general well-being, and somatic status were assessed as satisfactory. Local changes: improper head posture and restricted motion in the cervical spine. Palpation revealed hardening and thickening of the sternal end of the left clavicle and palpation-induced tenderness of the sternum and sternal end of the right 3rd rib. There were tenderness and mild edema

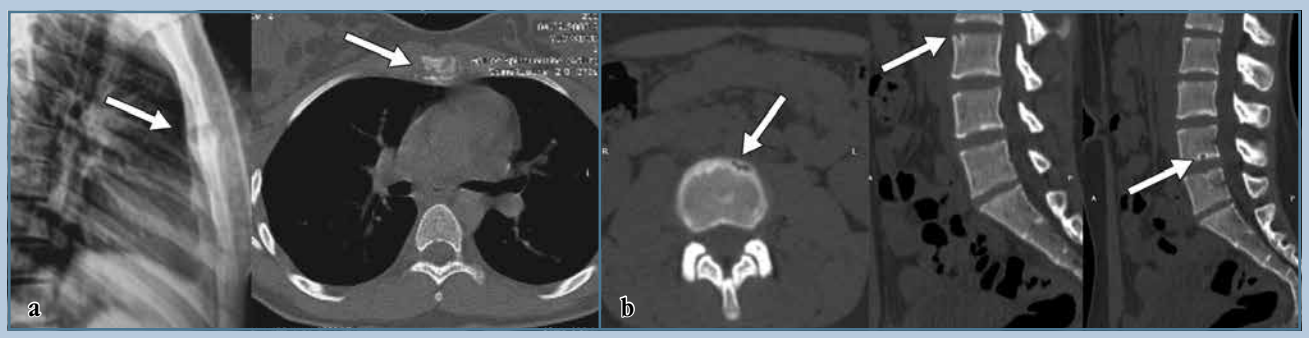

Fig. 5
Changes in the sternum and vertebrae in a 15-year-old female patient B.: **a** – a destructive lesion in the sternum, which is visualized on a lateral X-ray image and an axial CT slice; **b** – localized destructive foci with perifocal sclerosis in the superior subchondral portion of the L3 body and inferior portion of the L4 body

in the area of the anterior surface of the middle third of the tibia as well as tenderness to percussion in the C6–T4 area. MRI of the cervical spine (04.01.2014) demonstrated a deformity of the posterior portion of the C6 body without edema. The complete blood count revealed no abnormalities; the ESR was 15 mm/h; CRP was negative. According to the bone scan data, there was RT hyperfixation in the sternal end of the left clavicle and anterior segment of the left 4th rib. Given the medical history and laboratory and instrumental tests, the patient was diagnosed with chronic multifocal osteomyelitis and treated with pamidronic acid (30 mg per course), indomethacin (2 mg/kg/day), and quarterly courses of bisphosphonates. The treatment led to relief of the pain and recovery of the range of motion in the cervical spine. The indomethacin dose was reduced to 1.5 mg/kg/day; the administration interval of pamidronic acid was increased to 6 months. There were no complaints. Control MRI of the cervical spine (Fig. 7; 2 years after the treatment) revealed no changes over time: a reduced posterior portion of the C6 vertebral body without perifocal edema and destruction of the contacting disc. Given the complete clinical and laboratory remission as well as the lack of destructive progression, clinical symptoms, and laboratory changes, therapy was discontinued. The patient has been followed-up by a rheumatologist.

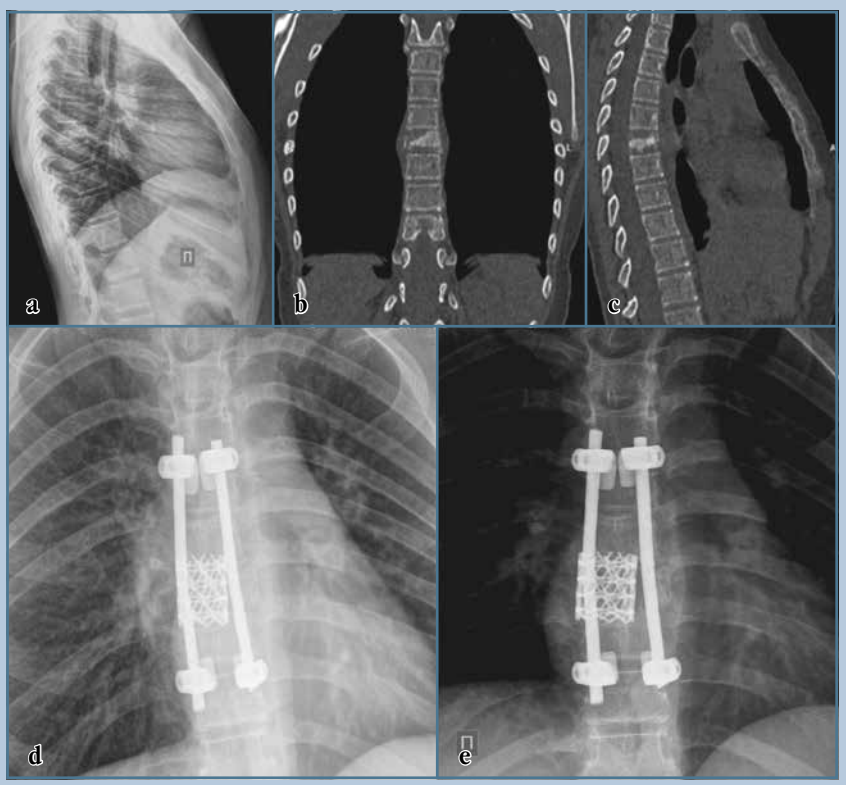

Fig. 6
Results of a radiographic study of a 10-year-old female patient P.: a lateral X-ray image **(a)**, coronary **(b)** and sagittal **(c)** CT slices of the spine before surgery; anteroposterior **(d)** and lateral **(e)** X-ray images after surgery (see explanation in the text)

Discussion

NBO is a relatively rare disease of children and adolescents, which is unfamiliar to surgeons and vertebrologists, but has long been described, in particular in the domestic medical literature [1 5].

Usually, the clinical picture of NBO presents with pain of varying severity in a certain skeletal segment, which may exacerbate at night and be accompanied by fever; local edema and an increase in the local temperature may develop. Despite the fact that the metaphyses of long bones and clavicles are predominantly affected, up to 20 areas of the skeleton, including the vertebrae that are the quite typical localization of the lesion, can be simultaneously involved in the pathological process [9].

The feature of vertebral NBO is a high rate of multifocal lesions with predominant involvement of the thoracic and cervical vertebrae and a monocyclic or recurrent course. Radiographic changes in the vertebrae in NBO are very diverse and can be represented both by destruction and sclerosis of the bone tissue and by vertebral deformity of varying severity, in particular by the deformity that is accompanied by spinal cord compression [6, 16] or leads to the development of spinal deformities, which is reflected in the classification of orthopedic complications of NBO [20]:

1) pathological fractures;
2) limb deformities;
3) spinal deformities (kyphosis, scoliosis, kyphoscoliosis);
4) bony growths/hyperostosis;
5) delay in axial growth, leading to shortening of a skeletal part/segment;
6) local delay (asymmetry) in growth.

Vertebral NBO is characterized by typical features including polymorphism of the clinical picture and non-specific laboratory changes. Like peripheral NBO, the process can be associated with various immunopathological inflammatory diseases: juvenile arthritis, psoriasis, uveitis, acropustulosis, gangrenous pyoderma, inflammatory bowel diseases (Crohn's disease and nonspecific ulcerative colitis), and acute febrile neutrophilic dermatosis (Sweet's syndrome); NBO is significantly less common in patients with granulomatous polyangiitis, Behçet's disease, and Takayasu aortoarteritis [7, 14, 18], which explains frequent diagnosis of concomitant diseases of the skin, joints, eyes, gastrointestinal tract, and lungs in NBO patients [20].

The differential set of NBO includes a wide range of diseases that are associated with the peculiarities of bone lesions, in particular with involvement or non-involvement of the vertebrae in the process (Table 4).

The diagnosis of the disease requires a large number of laboratory and instrumental tests, evaluation of complete blood count parameters and acute phase indicators, and obligatory radiographic imaging of the affected skeletal part. In this case, the changes that are detected during bone scanning and MRI and characterize primarily metabolic activity of the process may not be confirmed by X-ray and CT that reflect the severity of destruction or reactive changes. The final diagnosis is made based on the total morphological pattern of inflammation in the bone; in this case, specific and nonspecific bacterial osteomyelitis as well as malignant and benign bone tumors should be completely excluded [8]. That is why the bone biopsy followed by bacteriological and morphological studies is mandatory for the final verification of the disease.

NBO treatment is empiric in most cases; however, the data accumulated in recent years enable systematization and definition of the following sequence:

NSAIDs are considered first-line therapy drugs; however, if they are not enough effective, short courses of corticosteroids, methotrexate, sulfasalazine, colchicine, and azithromycin are used [9];

– bisphosphonates (inhibitors of osteoclast activity) are used to reduce pain [11], decrease the destruction focus in size, and control inflammatory activity in the bone, which is associated with their potent anti-inflammatory effect, the nature of which still remains not entirely clear; bisphosphonate therapy changes the ratio of pro-inflammatory and anti-inflammatory cytokines, in particular TNF-α and interleukin-6 [19];

– the use of inhibitors of TNF-α that is considered one of the steps in the development of NBO [12] is effective both in an isolated bone lesion and in NBO combined with comorbid immune-mediated diseases [12, 16]; in the case of a severe destructive process or another comorbid condition, TNF-α inhibitors can be combined with NSAIDs, basic anti-inflammatory drugs, and bisphosphonates.

The efficacy of NBO therapy is evaluated based on the achieved clinical remission, reduction in laboratory indicators, and absence of complications. Involvement of the spine in the pathological process and the presence of concomi-

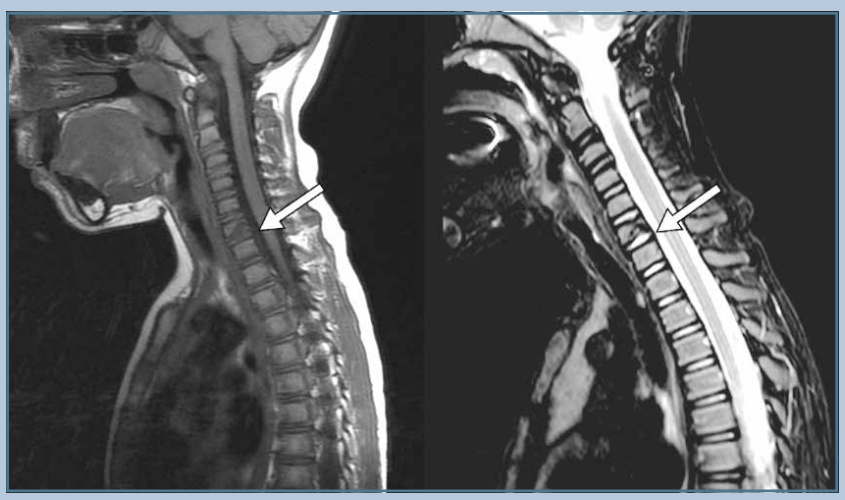

Fig. 7
A C6 lesion in the setting of multifocal non-bacterial osteomyelitis in the form of a destructive focus in the postero-inferior portion of the vertebral body

tant rheumatic disease crucially affect the choice of initial therapy. An analysis of the efficacy of different therapeutic regimens, including our data, demonstrates that bisphosphonates are the drugs of choice for vertebral NBO. They quickly suppress inflammation in bones, relieve pain, and prevent further destruction (for this reason, drugs from this group are widely used to treat osteolytic bone tumors and systemic bone dysplasia) [17].

Conclusion

NBO is a relatively rare auto-inflammatory skeletal disease typical of children and adolescents; its identification is actually the diagnosis of exclusion and requires diagnostic studies, among which the major ones are complex bacteriological and morphological studies of a substrate from the pathological area. Pathological material for analysis should be sampled from the most active focus, identification of which requires, in addition to a clinical and laboratory study, a comprehensive radiographic study.

Management of the patient with vertebral NBO should be interdisciplinary and involve doctors of various specialties: pediatricians, rheumatologists, orthopedists, surgeons, tuberculosis specialists, etc. In contrast to peripheral NBO, failure of NSAIDs in the case of vertebral NBO is the reason for early therapy with bisphosphonates (pamidronic acid-based drugs).

Surgical manipulations in NBO patients, including those with the vertebral form, should be carried out for diagnostic purposes, while surgery is advisable only in the case of disease complications. Complications of the vertebral form include segmental instability with severe pain and/or spinal deformity.

The lack of appropriate protocols and standards is a major problem in the diagnosis and treatment of NBO; their algorithmization may significantly improve disease outcomes and patients' quality of life and minimize the indications for surgery and its amount.

Table 4
Differential set of vertebral and peripheral non-bacterial osteomyelitis [20]

Vertebral NBO	Peripheral NBO
Spondylitis:	Generalized specific infections affecting bones (brucellosis, syphilis,
a) infectious nonspecific;	tuberculosis).
b) specific tuberculous.	Leukemia.
Benign and malignant bone tumors.	Metastatic bone tumors.
Osteoporosis:	Histiocytosis.
a) juvenile idiopathic;	Hypophosphatasia.
b) glucocorticoid-induced.	Osteopetrosis.
Osteochondropathy (Scheuermann's disease).	Aseptic necroses.
Juvenile ankylosing spondylitis (Bekhterev's disease).	Juvenile arthritis.
Spondyloepiphyseal dysplasias.	Skeletal dysplasias.
	Fibrous cortical defect (nonosteogenic fibroma of bone).

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