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PEDIATRIC CLINIC
Department of Immunology, Allergology and Rheumatology

DISCHARGE SUMMARY WITH EPICRISIS

Name and Surname:	**LENKA PARIPOVIC**	Address:	**NOVI SAD, STRAZILOVSKA St. 4A**
Unique Citizen ID No:	**0405011805000**	Telephone:	
Date of birth:	**4 May 2011**	Register number:	**4917/2020**
Admission date:	**29 May 2020**	Discharge date:	**18 June 2020 13:00**

Condition at discharge: Cured

Diagnosis: **Osteomyelitis multifocalis chronica in obs. M863**

Therapy:
Brufen syrup 200mg/5 ml 5.5 ml every 6hrs continually
Controloc pills a 20mg 1 pill in the morning + ½ pill in the evening
Bactrim syrup 2x10 ml per day, for seven days
Probiotic capsules 1x1 capsule per day
Ursofalk capsules 1x1 capsule per day

Follow-up checkup:
Medical checkup in seven days, when the following will be done: CRP, Full blood analysis le dif,Trc
In one month, perfrorm a control MRI of left ankle and foot
Follow-up checkup by orthopedist with MRI results

In two months, do control test for vitamin D, PTH

Medical case history – Epicrisis

The girl became ill a month before admission, with development of pain and swelling in the left ankle, local therapy with sports creams for injuries was administered, and the swelling and pain receded within seven days. After that, she went to a training session and again felt pain in the same spot, to the touch of the lateral malleolus of left ankle. She was examined by an orthopedist, an MRI scan was done of the left ankle. Epiphysiolysis of the lateral aspect of the metaphysis of the distal end of the left fibula Salter-Harris fracture type II, without dislocation. Epiphysiolysis of both the anterolateral and the anteromedial aspects of the metaphysis, the distal end of the left tibia Salter-Harris fracture type II, without dislocation. Stress fracture dominant in the 2nd base and milder in the 3rd metatarsal bone of the left foot, Jones fracture without dislocation), and an X-ray of left ankle: a triangle-shaped shadow in the area of distal metaphysis of fibula, which is in direct contact with the epiphyseal plate, above which there is a detectable soft tissue edema,

without unambiguous pathological calcifications nor periosteal reaction. Recommendation given was to continue observation. Three weeks from the start of illness, she became febrile to 39° C with shivers, during the spike in temperature the following lab tests were done: on 24 May, showing elevated values of parameters for acute phase of inflammation (CRP 97 mg/l, WBC 15.4 G/l with the percentage of segmented granulocytes at 85%)." Pancef" medication was introduced, after which increased temperature with intermittent spikes persisted, but peaks were happening at 8-hour intervals and the girl's general condition was improved. As fever and acute phase reactants of inflammation persisted, an immunologist was consulted, additional tests were done of ANA, ANCA, aCLA, Beta-2 glycoprotein, test results came back unremarkable. "Cefriakson" medication was introduced, but as the fever and high parameters of inflammation persisted, and on the basis of anamnestic data on the pain and the swelling of the ankle, she was referred to the Institute with suspected osteomyelitis. She was examined by a pediatric surgeon, an X-ray of the left ankle was done after which the pediatric surgeon eliminated the possibility of bone infection, then the girl was examined by an immunologist, who indicated hospitalization for further diagnostics and treatment.

She had been training judo for three years, up until February this year, without any of the mentioned health issues, with no pain in her left ankle. At that time she had a swelling in her left ankle, which was sensitive to pain exclusively to the touch and when resting, but with no pain during walking or physical activity. She was examined by an orthopedist. The condition subsided one week later.

Epidemiological anamnesis on contact with anyone infected with Covid-19 is negative.

IgM and IgG for SARS COV 2 are negative for both the father and the child. Nasopharyngeal swab (PRC) for SARS COV 2 for the father and the child: negative.

Apart from the above stated, she has never had any serious illness, never undergone surgery.

She is the first child from a first, regularly monitored pregnancy which progressed unremarkably, was completed to term, and with a C section delivery. Antenatal and perinatal anamnesis are unremarkable. She was fed naturally for 13 months, mixed food was introduced as per advice by a pediatrician. Previous growth and development are unremarkable. Was regularly vaccinated. No allergic reactions to any food thus far. She had hives (urticaria) and was treated with amoxicillin in 2015, no allergy tests were done for drug hypersensitivity

Family medical history is negative with respect to hereditary diseases.

On admission, a 9 year old girl, in good general condition, conscious, responsive, body temperature 38.4° C, P 129, R 18/min, SaO2 100%, body mass 30kg (z-score 0), body height 140cm (z-score +1), BMI 15.26 (z-score 0). Normal gait pattern. Skin turgor and elasticity preserved, with no pathological efflorescence. Skin pinkish, with no pathological efflorescence. Lymph nodes in predilection sites not palpable. Pupils isochoric, symmetrically responsive. Eyeballs and conjunctiva mobile. Nasal passage clear. Pharynx hyperemic. Neck cylindrical, freely mobile within the physiological scope of movement. Torso properly aligned, symmetrically mobile in respiration. Auscultatory findings of the heart and of the lungs unremarkable. The abdomen is soft, below the level of the rib cage, no tenderness to palpation, liver and spleen not palpable. External genitalia are female, unremarkable. Rheumatological findings unremarkable. Normal gait pattern. Neurological findings unremarkable. Meningeal signs negative.

Erythrocyte sedimentation rate (ESR) 100 mm/h, CRP 74.3 mg/L, Fibrinogen 7.7 g/l, Procalcitonin within normal range, WBC 9.0 G/l, (seg 0.7, lymphocytes 0.17, monocytes 0.05), Er 4.23 T/l, HGB 126 g/l, HCT 0.35, Trc 462 G/L. APTT 37.8 s (24-35), APTT(R) 1.26 (0.7 – 1.2), PT 14.8 s (10.0 – 13.1), INR 1.33. Mix test APTT mix (s) before incubation 35 sec, APPT mix (R) before incubation 1.170 R, APPT mix (s) after incubation 37.1 sec, APTT mix (R) after incubation 1.250 R, PT (s) before incubation 12.5 sec, PT (INR) before incubation 1.130, INR, PT (s) after incubation 12.7 sec, PT (INR) after incubation 1.150 INR
Peripheral blood smear: unremarkable morphology in elements of all three cell types.

Total Protein, Albumin, Urea, Creatinine, Uric Acid, CPK, Amylase, Lipase, ALT, GGT, LDH, Na, K, Ca, Mg – within reference values. Glucose 6.41 mmol/L (3.33 – 5.55), Cl 95 mmol/L (98 – 108), AST 0.64 ukat/L (0.08 – 0.43), C3 2.06 g/L (0.8 – 1.5), C4 0.5 g/L (0.1 – 0.4), IgM 1.17 g/l (ref.values 0.40 – 1.6), IgG 10.78 g/l (r.v. 7 – 14), IgA 2.65 g/l (r.v. 0.51 – 2.9), IgE 116 HIU/ml (r.v. up to 100).

Factor VIII, Von Wilebrand in ref.values, factor IX 169% (r.v. up to 150). Ferritin 239 ug/L (r.v. up to 120), T3, T4, TSH within reference values, Anti-TPO (TgAb) 5.48 IU/ml (r.v. up to 4.1), Cu, Homocysteine – within normal values, Vit D 113 mmol/l, PTH 5.3 pg/mL (r.v. 14 – 87), Beta-CrossLaps (B-CTx) 1606 pg/ml.

Enzyme screening test, Coombs tests – negative. ASTO, Waler Rose, Latex RF – negative. ANA negative. ANCA negative. aCLA, beta 2 glycoprotein, anti CCP – within ref.values. HLA B 27 in work.
Throat and nose swab negative. IgM, igG Borelia Burgdorferi negative.

Coproculture Jersinia, Campylobacter negative. Candida spp. isolated in stool.

HBsAg, Anti-HCV negative.

Hemoculture in febrility 3x negative.

Urine: ketones 1, rest of the findings unremarkable.

X-ray of heart and lungs unremarkable. PPD 3 negative.

ECG and cardiologist's findings: Physical examination of the heart: heart action is rhythmical, tones are clear, murmur is not heard. ECG: normogram, sinus rhythm, frequency 105/min. Focal block of right bundle branch. Within physiological limits.
Echocardiography Findings: Situs solitus. Venous drainage unremarkable. LA diameter 16mm. IAS intact. MV normal morphology, normal flow profile. TV normal size and morphology, normal flow prfile. AV harmonious. Left ventricle dimensions: LVD 33mm, LVS 23mm, FS 0.30, s 8 mm, zz 6 mm). DV unremarkable cavum diameter (12 mm in diastole). IVS intact. VA harmonious. Ao tricuspid, diameter at annulus 15mm, unremarkable speed and profile flow. The ascending aorta – nothing abnormal detected. Aortic arch left, branches – nothing abnormal detected. Descending aorta is of unremarkable morphology, normal speed and (pulsatile) flow profile. PA is of unremarkable dimensions (20mm at annulus), normal speed and flow profile. PA branches – nothing abnormal detected. Pericardium – nothing abnormal detected. Both coronary arteries have unremarkable morphology, with unremarkable arising, uniform in diameter (LCA 3.5mm, DCA 3.6mm). The medical finding is unremarkable.

Ultrasound of the abdomen (29 May 2020): the liver is homogeneous in echotexture and of unremarkable dimensions. Cholecystis /gall bladder is somewhat distended, cholecystic wall thickness less than 3mm. A concrement 11mm in diameter is showing in the cholecystic lumen, casting a visible acoustic shadow. Bile ducts are not dilated. The pancreas is of unremarkable dimensions, with homogenous echotexture. The spleen has smooth contours, homogeneous echotexture, dimensions 86x25mm. Both kidneys are of unremarkable shape and size, with preserved parenchymal width, clear corticomedullary borders, with no dilation in the PK system. Both adrenal chambers are unremarkable. There are no visible pathological changes on the walls of the partially distended urinary bladder. No visible presence of free fluid in the abdomen. The appendix is not discernible.

Ultrasound of hips, knees and ankles: synovial cavities of both hips – no leakage. Recesses of both knees – no visible presence of leakages.

CT scan of both shins and feet: computerised tomography was performed of the distal end of both shins and both feet, with a series of axial slices natively without applying intravenous contrast. Present artifacts limited the evaluation of the examination. Thus conducted examination identified the following : – presence of irregular lytic lesion within the posterior aspect of the lateral malleolus of the left fibula,

approximate dimensions 12 x 7 x 11 mm (AP X LL X CC diameter), which in part thins out and in part disrupts the continuity of the cortex itself, with no presence of periosteal reaction. – At the border between the distal part of the diaphysis and the distal part of the epiphysis of the left tibia, there is an oval lytic dissolution, approximate dimensions 5 x 4 mm, with an evident zone of sclerosis. – A change of the same CT characteristics and localization (at the border between the distal part of the metaphysis and the distal part of the epiphysis) in the right tibia, approximate dimensions 7 x 9 x 9 mm (AP x LL x CC diameter), which disrupts the continuity of the epiphysis and with a visible partial zone of sclerosis, without visible periosteal reaction. – Bilateral thinning of bone baulk in the talus and the calcaneus – Signs of pathological fractures are not visible – thus done CT scan does not show changes within the soft tissues of the distal part of tibia and fibula bilaterally. CONCLUSION: the identified multifocal zones of bone thinning are of insufficiently specific CT characteristics, considering the localization of the distal part of the metaphysis and the distal part of the diaphysis of the tibia bilaterally and of the fibula (lateral malleolus to the left). Options for a differential diagnosis are changes as a consequence of an infection, NOF, chondroblastoma, GCT. Recommendation: MRI examination of these regions and/or a biopsy and PH verification.

MRI of the left ankle: comparison with the MR examination of the left ankle dated 19 May 2020. In today's examination, a relatively unchanged appearance is noted of the bone marrow edema zones in the region of distal metaphysis of the tibia and fibula, immediately adjacent to the epiphyseal plate, within which there are noticeable oval- and round- shaped areas of osteolysis, partially bordered by an edge of sclerosis, the largest of which is in the fibula, of less than 11mm in diameter. The cortex of the lesion localized in the fibula is mildly thinned, without erosion and extension into the soft tissues. The adjoining edema of the soft tissues and of the periosteum next to the lateral malleolus is less extensive. Unchanged is the appearance of the bone marrow edema of the proximal metaphyses I – IV bones, without clearly defined areas of ostelolysis. The presented joint spaces are without any significant leakages or synovial proliferation. There are no noticeable areas of acute fractures in the presented skeleton, nor of nodular changes in soft tissues. Tendons and ligaments in this region do not manifest any changes. Conclusion: correspondingly to the distribution and symmetry of the osteolytic zones bordered by sclerosis in the distal fibula and tibia, the differential diagnosis would consider primarily a chronic, recurrent osteomyelitis (CRMO). Considering that the MR results are not pathognomonic for this entity a biopsy is required of the change in the left lateral malleolus, in order to dismiss potential histiocytosis and hematologic malignancies.

Scintigraphy: in scintigrams, in the arterial phase there were not noticed any zones of pathological collection of radiopharmaceuticals (increased blood flow is not noticed), while in the tissue phase there was noticed symmetrical, linear intensified collection in the projection of the distal fibula and tibia bilaterally, which corresponds to the zone of epiphyseal growth (which is common for the patient's age). In delayed scintigrams of the whole body, physiologic distribution of radiopharmaceuticals was noticed. In targeted scans of feet, minor focus was noticeable in the projection of the 3rd metatarsal bone right, while changes that had been observed in the MRI of the left foot and shin were not noticeable scingigraphically. Opinion: resulting scintigrams show a conventional collection of radiopharmaceuticals in all three phases, with the distinction of a minor focus in the projection of the 3rd metatarsal bone to the right, which was noticed in the delayed targeted scintigram (changes observed in MRI of the left foot and shin were not noticeable scintigraphically = medical findings are without clear scintigraphic indicators which would be pointing at the presence of osteomyelitis.

Orthopedist's findings: Reason for consultation was because of verified changes in the metaphysis of the right tibia and fibula as well as of the left tibia. CT report attached. The child continues to experience spikes of increased body temperature despite antibiotic therapy. As part of further diagnostics, bone scintigraphy and MRI examination of both ankles have been scheduled. Following the mentioned diagnostic procedures, another option is to do a biopsy of the change in the posterolateral aspect of the distal metapsysis of the

fibula, as well as biopsy of the bone marrow. Follow-up visit after completed diagnostic procedures, or earlier if needed.

Hematologist's findings: Girl aged 9, hospitalized due to fever of unknown origin, with high acute phase reactants of inflammation and changes in the distal part of the left shin indicating an inflammation process. Lab results: ESR 100, CRP elevated, fibrinogen as well. In the Full Blood Analysis (Complete Blood Count), total leucocytes are within normal parameters leaning towards mild leucocytosis with neutrophilia, elements of the red blood cells are at the bottom of the normal range, Tr 459 G/l. X-ray results of lungs and heart were unremarkable, as well as the ultrasound of the abdomen together with intestinal wall thickness. CT examination of shins: Identified multifocal zones of bone thinness in the metaphysis of right tibia and fibula as well as left tibia, which are of insufficiently specific CT characteristics. I recommend a Skeletal System Scintigraphy, biopsy of the accessible bone change, APKS. Further tests pending the results obtained.

Endocrinologist's findings: Negative anamnesis on multiple, recurrent and "significant" fractures (compressive spinal fractures and more than 2 other bone fractures) with regard to both the current condition and therapy which might lead to decreased bone density. (Was) actively involved in sports. Unremarkable skin and adnexa cutis, sensory functions unremarkable. No dysmorphia. Growth and development normal. Current body height is at 75th percentile. In previous laboratory tests: dynamic changes in acute inflammation reactants; thyroid, adrenal and endocrine pancreatic functions – unremarkable; Ca, P and ALP at normal levels; Mg in serum high-normal values; vitamin D in serum high-normal values; PTH serum – mildly suppressed; crosslaps unremarkable for her age. Ferritin elevated. Based on the medical history/anamnesis, on the clinical course and on previous analyses, further differential-diagnostics algorithm should ensure exclusion of granuloma diseases and primary disorders in bone and cartilage tissues. I recommend DEXA, homocysteine and Cu in serum. From the endocrinological point of view, at this time: discontinue any products containing vitamin D + sufficient hydration of the organism (the lab. results received thus far are most commonly caused by increased daily intake of vitamin D, during and after immobilization); Other conditions, e.g. athlete energy deprivation syndrome, are less probable anamnestically, and the diagnosis of juvenile idiopathic sclerosis is ex juvantibus. Further consultation with an endocrinologist as needed and per indications of practicing physicians.

Upon admission, dual antibiotic therapy was introduced with Ceftriaxone and Clindamycin together with a probiotic supplement, on the same day administration of Ceftriaxone was stopped and Ceftazidime was introduced. During the first two days of hospitalization, she was febrile, and from the third day she was subfebrile. In temperature spikes, she was administered Brufen (Ibuprofen) syrup / Paracetamol syrup, which brought the temperature down. Throughout the period of hospitalization, she was administered ursodeoxycholic acid because of deposits in her gallbladder. The therapy applied resulted in improvement of the child's general condition and decrease in acute phase reactants and her body temperature normalized, however, on the fifth day of hospitalization she again became febrile with temperature spikes 2x a day, and a mild increase of acute phase reactants of inflammation. Blood cultures were done and results came back negative, so the antibiotic therapy was replaced by Meropenem and Vancomycin, however as temperature spikes persisted, additional examinations were done, an orthopedist was consulted, a CT scan was done of both ankles, after the results came in of multifocal zone of bone thinness in the metaphyses of the right tibia and fibula as well as the left tibia, an MRI of the left ankle was also done as well as a skeletal scintigraphy, and NSAID ibuprofen was introduced in anti-inflammatory doses, along with protection of the gastric membrane. The applied therapy resulted in improvement of the child's general condition, normalization of body temperature and normalization of acute phase reactants.

Follow-up control laboratory results: CRP 1.1 mg/l, WBC 5.9 G/L (neu 43%, lymf 47.7%), Erc 3.96 T/L, Hgb 118 g/l, Hct 0.33, Trc 338 G/L. PT, aPP – within reference values. Glycemia, total proteins, albumins,

urea, creatinine, acidum uricum, ALT.gama GT, LDH – within reference values. AST 0.640 ukat/l (r.v. less than 0.43). Urine without pathological impurities.

Follow-up control findings by orthopedist: the child is in good general condition. She has been afebrile for ten days. Local findings unremarkable. Decrease in infection parameters. Bone scintigraphy is attached, describing focal points which may correspond to osteomyelitis. Considering the clinical improvement, there is no absolute indication for biopsy for now. Continue therapy with NSAID. Schedule a follow-up MRI scan one month from now. Follow-up visit with MRI scan results as well as if the clinical situation worsens.

She is discharged to home in good general condition with advice given on further therapy and follow-ups.

On the basis of the anamnestic data, the lab results, the CT, MRI scans findings and the clinical course of the disease, we are of the opinion that the girl most probably suffers from multifocal recurrent chronic osteomyelitis, the confirmation or dismissal of which would necessitate a biopsy of the bone changes and a PH verification, which was postponed due to good response to the applied therapy, however, other etiologies of disease must not be dismissed, therefore further observation of the child and regular follow-up visits are necessary, and, in consultation with the orthopedist, consensus on future diagnostics and treatment.

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