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CASE REPORT PRIKAZ BOLESNIKA

CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS (CRMO) OF PELVIS AND SPINE IN A PAEDIATRIC PATIENT – A CASE REPORT

KRONIČNI REKURENTNI MULTIFOKALNI OSTEOMIJELITIS (KRMO) ZDJELICE I KRALJEŽNICE U PEDIJATRIJSKOG BOLESNIKA – PRIKAZ BOLESNIKA

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Abstract

Chronic recurrent multifocal osteomyelitis (CRMO), which is the most serious type of chronic nonbacterial osteomyelitis (CNO), is a rare chronic noninfectious auto-inflammatory disease characterized by multiple sites of painful bone inflammation. Its etiology and pathophysiology is still unclear. The clinical presentation of CRMO is discerned by bone pain with typical inflammation signs and elevated inflammation parameters. Lytic and sclerotic bone lesions can be found on X-ray scans, computed tomography (CT) and magnetic resonance imaging (MRI), but magnetic resonance imaging represents a more sensitive method of choice for determining the prognosis and stage of the disease. CRMO treatment methods include the use of non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, bisphosphonates and biological therapy. In 2019, a 13-year-old boy was admitted at the University Hospital Center Zagreb (UHC Zagreb). After several years of disease remissions and exacerbations with constant moderate pain, the correct diagnosis has been ascertained through the use of imaging methods, clinical presentation, biopsy and the exclusion of other diagnoses, The patient was monitored by a paediatric rheumatologist, and he has remained in remission following his treatment with biological therapy. CRMO should be suspected in a child with chronic and recurrent bone pain, elevated inflammatory parameters, osteolytic and osteosclerotic lesions found on X-ray, with the addition of visible bone oedema detected through MRI and the exclusion of infectious or malignant etiology. The process of establishing proper diagnoses puts an end to the unnecessary diagnostic procedures and inadequate therapy and reduces the occurrence of disease complications. This case report could potentially prove to be helpful in establishing a

proper diagnosis and treatment of patients with CRMO, but new studies about this rare and important disease would help shed some light on this topic and provide more information about this disease.

Keywords: CRMO, chronic recurrent multifocal osteomyelitis, paediatric patient, inflammation of lumbosacral spine, autoinflammation

Sažetak

Kronični rekurentni multifokalni osteomijelitis (KRMO) koji je najteži oblik kroničnog nebakterijskog osteomijelitisa (KNO) rijetka je kronična neinfektivna autoinflamatorna bolest koju karakteriziraju višestruka mjesta upale kostiju. Etiologija i patofiziologija bolesti još uvijek je nejasna. Klinički dijagnoza KRMO-a razabire se po boli u kostima i prisutnosti tipičnih znakova upale uz povišenje parametara upale. Litičke i sklerotične lezije kostiju mogu se naći na rendgenskim snimkama, pregledu kompjuteriziranom tomografijom i nuklearnoj magnetskoj rezonanciji (NMR), a za proširenost i fazu bolesti magnetska rezonancija predstavlja osjetljiviju metodu izbora. Bolest se liječi različitim protuupalnim lijekovima, kao što su nesteroidni antireumatici (NSAR), glukokortikoidi, bisfosfonati i biološki lijekovi. Dječak star 13 godina primljen je 2019. godine u Klinički bolnički centar Zagreb (KBC Zagreb). Nakon višegodišnjih remisija i egzacerbacija bolesti uz stalnu umjerenu bol, slikovnim dijagnostičkim metodama, kliničkom slikom, biopsijom i isključenjem drugih dijagnoza, postavljena je dijagnoza KRMO. Bolesnik je pod nadzorom dječjeg reumatologa i nakon biološke terapije ima zadovoljavajuću remisiju bolesti. Na KRMO treba posumnjati u djeteta s kroničnim i ponavljajućim bolovima u kostima, povišenjem upalnih parametara, osteolitičkim i sklerotičkim lezijama na rentgenskoj (RTG) snimci, uz vidljiv koštani edem na NMR-u i isključenom infektivnom ili malignom etiologijom. Postavljanjem ispravne dijagnoze prekidaju se nepotrebni dijagnostički postupci i neadekvatna terapija te se smanjuju komplikacije bolesti. Ovaj prikaz slučaja mogao bi biti koristan u dijagnosticiranju i liječenju bolesnika s KRMO-om. Nova istraživanja o ovoj rijetkoj, ali važnoj bolesti pomogla bi nam da saznamo više informacija o ovoj bolesti.

Ključne riječi: KRMO, kronični rekurentni multifokalni osteomijelitis, pedijatrijski bolesnik, autoinflamacija, upala lumbosakralne kralježnice.

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO), which is the most serious type of chronic nonbacterial osteomyelitis (CNO), is a chronic noninfectious autoinflammatory disease characterized by multiple sites of painful swelling of bones, most often in the metaphysis of the long bones or the pelvis, the shoulder girdle and the spine, although every bone can be involved (1). This little-known inflammatory bone disease appears mainly in children, and the mean age at its onset is approximately 10 years of age. The epidemiology of the disease depends on the studies, and its prevalence is estimated to be between 1/160 000 and 1/2 000 000, while its incidence is estimated to be between 1/250 000 and 1/1 000 000. Females are more affected by this disease than males, in a ratio of 4:1 (2).

Even though the exact mechanism of CRMO is unknown, several studies have made assumptions about its etiology and pathophysiology. It has a complex genetic background related to innate immunity combined with the effects of many epigenetic mechanisms, such as intestinal dysbiosis and stressor exposure (3). Also, similarities with juvenile spondyloarthritis were reported, moreover the fact that the evolution from one disease to another is not impossible (3). The cases can be divided into sporadic form and syndromic form. In syndromic forms CRMO is linked with Majeed syndrome which is an autosomal recessive hereditary disease. It is characterized by CRMO in early age

UVOD

Kronični rekurentni multifokalni osteomijelitis (KRMO, na engl. *chronic recurrent multifocal osteomyelitis*, CRMO) koji je najteža vrsta kroničnog nebakterijskog osteomijelitisa (KNO, na engl. *chronic nonbacterial osteomyelitis*, CNO), kronična je neinfektivna autoinflamatorna bolest koju karakterizira višestruko bolno oticanje kostiju, najčešće u području metafize dugih kostiju ili zdjelice, ramenog obruča i kralježnice, iako može biti zahvaćena svaka kost (1). O ovoj autoinflamatornoj bolesti kostiju ne zna se mnogo toga, a javlja se pretežno u djece oko desete godine života. Epidemiologija bolesti razlikuje se od studije do studije, prevalencija bolesti se procjenjuje na između 1:160 000 u općoj populaciji i 1:2 000 000 u općoj populaciji, a incidencija bolesti na između 1:250 000 u općoj populaciji i 1:1 000 000 u općoj populaciji. Ova bolest češća je u žena nego u muškaraca i to u omjeru 4:1 (2).

Iako je točan mehanizam KRMO-a nepoznat, u nekoliko studija navode se pretpostavke o etiologiji i patofiziologiji te bolesti. Ova bolest ima složenu genetsku pozadinu povezanu s urođenim imunitetom u kombinaciji s učincima mnogih epigenetskih mehanizama, kao što su crijevna disbioza i izloženost stresorima (3). Uz to, zabilježene su sličnosti s juvenilnim spondiloartritisom, to jest, otkriveno je da postoji mogućnost da jedna bolest evoluira u drugu (3). Bolest se javlja u sporadičnom i sindromskom obliku. U sindromskim oblicima bolesti KRMO se povezuje s Majeedovim sindro-

and dyserythropoietic anemia which is often followed by recurrent fever. Furthermore, it is connected with an absence of the Interleukin-1 Receptor Antagonist (DIRA) that is an autosomal recessive disorder which occurs in newborns with osteitis, generalized pustulosis, periostitis and systemic inflammation as a consequence of mutations in the interleukin-1 receptor antagonist (IL1RN) (4,5). In sporadic forms of CRMO a genetic component is suspected, particularly in the dysregulation of immune pathways of the anti-inflammatory cytokine interleukin-10 and pro-inflammatory cytokine interleukin-1 (5). It is worth mentioning that several adult-onset forms of this disease have been reported. These disease types simulate the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) (5). It is not clear whether the SAPHO syndrome and CRMO are two separate entities or if they are part of the same disease spectrum with CRMO being the pediatric parallel of the SAPHO syndrome (6).

A typical symptom of CRMO is bone pain which is worse during the night and is often accompanied by fever (7). From one to approximately 20 locations can be entangled at the same time. The metaphysis of the long bones, the clavicles, and the vertebral bodies are the most common sites. Moreover, other locations, such as the pelvis, the mandible, and the small bones of the hands and feet can also be involved (8). Clinical signs include standard sings of inflammation: *rubor, tumor, calor, dolor* and *functio laesa* of the affected bone. These signs can also be found on the skin above the affected bone. Optional symptoms can be precipitated by paraosseous inflammation, involving peripheral nerves and vessels. A few other inflammatory conditions are often associated with CRMO such as psoriasis and palmoplantar pustulosis (8%), inflammatory bowel disease (10%), severe acne (10%), ankylosing spondylitis (25%) and the aforementioned juvenile spondyloarthritis (3,4). Infectious osteomyelitis, malignancy (osteosarcoma, Ewing's sarcoma, leukemia, non-Hodgkin lymphoma), benign bone lesion (such as osteoid osteoma) and Langerhans cells histiocytosis (LCH) are the most common differential diagnoses (9). In diagnosis, a combination of clinical, radiological and histological findings are used. Due to the absence of disease biomarkers or widely used criteria, CRMO still remains a diagnosis of exclusion. Laboratory tests often reveal modest leukocytosis, faster erythrocyte sedimentation rate (ESR) and slightly elevated other inflammation parameters, but normal findings are also possible. Cultures of bone and hemocultures are almost never positive. Imaging techniques are significant for the diagnosis of CRMO and the exclusion of other differential diagnoses. The first approach includes plain radiographs (X-ray) through which bone changes can be seen as radiolucent, osteo-

mom koji je autosomna recesivna nasljedna bolest. Neke od značajki ove bolesti su pojava KRMO-a u ranoj dobi i diseritropoetska anemija uz koju se često javlja povratna vrućica. Nadalje, povezuje se s nedostatkom antagonista interleukin-1 receptora (DIRA) koji je autosomno recesivni poremećaj koji se javlja u novorođenčadi u obliku osteitisa, generalizirane pustuloze, periostitisa i sustavne upale kao posljedica mutacije antagonista interleukin-1 receptora (IL1RN). (4,5). U sporadičnim oblicima bolesti KRMO sumnja se na genetsku komponentu, osobito u disregulaciji imunoloških putova protuupalnog citokina interleukina-10 i proupalnog citokina interleukina-1 (5). Bitno je spomenuti da je zabilježeno nekoliko oblika bolesti koji su se javili u odrasloj dobi. Ove vrste bolesti javljaju se kao sindrom SAPHO (sinovitis, akne, pustuloza, hiperostoza i osteitis) (5). Još uvijek ne možemo sa sigurnošću odrediti jesu li sindrom SAPHO i KRMO dva odvojena entiteta ili su dio istog spektra bolesti pri čemu je KRMO pedijatrijska inačica sindroma SAPHO (6).

Jedan od tipičnih simptoma KRMO-a je bol u kostima koja je jača noću i često se javlja uz vrućicu (7). Istovremeno može zahvatiti i do 20 područja. Najčešće zahvaća sljedeća područja: metafize dugih kostiju, ključne kosti i trupove kralješaka. Također mogu biti zahvaćena i druga područja, poput zdjelice, donje čeljusti i malih kostiju šaka i stopala (8). Klinički znakovi uključuju klasične znakove upale: crvenilo (*rubor*), otok (*tumor*), toplinu (*calor*), bol (*dolor*) i gubitak funkcije (*functio laesa*) zahvaćene kosti. Ovi se znakovi mogu primijetiti i na koži povrh zahvaćene kosti. Ostale moguće simptome može uzrokovati upala koju karakterizira bujanje koštane srži, a uključuje periferne živce i krvne žile. Postoji nekoliko drugih upalnih bolesti koje se često povezuju s KRMO-om kao što su psorijaza i palmoplantarna pustuloza (8 %), upalna bolest crijeva (10 %), teški oblici akni (10 %), ankilozantni spondilitis (25 %) i prethodno spomenuti juvenilni spondiloartritis (3,4). Infektivni osteomijelitis, maligne bolesti (osteosarkom, Ewingov sarkom, leukemija, ne-Hodgkinov limfom), benigne koštane lezije (kao što je osteoidni osteom) i histiocitoza Langerhansovih stanica (na engl. *Langerhans cells histiocytosis*, LCH) najčešće su diferencijalne dijagnoze (9). Za postavljanje dijagnoze upotrebljavaju se kombinacije kliničkih, radioloških i histoloških pretraga. Zbog nepostojanja biomarkera bolesti ili najčešće korištenih kriterija, KRMO je i dalje dijagnoza isključenja. Laboratorijske pretrage često otkrivaju umjerenu leukocitozu, bržu sedimentaciju eritrocita (ESR) i blago povišene ostale upalne parametre, no moguće je i da nalazi budu s normalnim vrijednostima. Nalazi kultura kostiju i hemokultura gotovo nikada nisu pozitivni. Tehnike snimanja iznimno su bitne za dijagnosticira-

lytic, or sclerotic lesions, with the possibility of no changes being detected in the early stages of the disease. Magnetic resonance imaging (MRI) is the golden standard technique with high sensitivity, especially in the early stages of the disease. Typical findings include bone oedema, which is also the first sign of the disease, which is most commonly followed by osteolytic or sclerotic, and hyperostotic bone lesions, as well as periosteal and soft tissue reactions, if present. Infectious osteomyelitis and malignant bone tumors are ruled out by bone biopsy (10,11).

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment, with reported response rates of up to 80% (12). Oral steroids, methotrexate, sulfasalazine, colchicine, bisphosphonates and tumor necrosis factor (TNF)-alpha inhibitors can be used as an alternative treatment in cases in which patients are unresponsive to NSAIDs, during exacerbations and in order to prevent relapses. The anti-inflammatory action of azithromycin may also contribute to a positive clinical therapeutic effect (13). In this paper, we present a case of a 13-year-old boy who suffered from pain in the lumbar spine and who has received the final diagnosis of CRMO at the University Hospital Center (UHC) Zagreb. Our aim is to contribute to the avoidance of misdiagnoses and late diagnoses of this disease.

CASE REPORT

We were introduced to a case of a 13-year-old boy, suffering from pain projecting into the lumbosacral region of his spine since the age of 7. The pain was precipitated by a trauma which happened in 2013, during a physical education class (PE) (forward roll). When it comes to the patient's anamnesis vitae it can be noted that there were no difficulties reported during his birth, and the APGAR score at birth was 9/10. Before this event, the boy did not suffer from any diseases until the age of 7. In 2013, the patient was hospitalized because of pain in the lumbar spine. After an MRI showed a minimal discontinuation of the left mass of the lateral sacral bone in the level of S1 without significant displacement and with the presence of bone oedema, the fracture of sacral bone was suspected (Figure 1, 2A, 2B, 3). He was discharged under the diagnosis of unknown etiology back pain and pharmacotherapy in terms of analgesia and physical therapy were prescribed. Because of the presence of mild pain, which did not progress to severe or limiting levels, the patient underwent physical therapy at least once a year until 2017, when the diagnosis of scoliosis was made after general medical examination. During that period, the exacerbation of pain also occurred.

After five years, the boy was hospitalized due to anaemia and malnutrition and after a short period he was discharged with a recommendation of taking iron

nje KRMO-a i isključivanje drugih diferencijalnih dijagnoza. Prvi pristup je obična radiografija (rendgenska) u kojoj se promjene na kostima mogu vidjeti kao radiolucentne, osteolitičke ili sklerotične lezije, bez promjena u ranim fazama bolesti. Magnetska rezonancija (MR) metoda je koja predstavlja zlatni standard s visokom osjetljivošću, osobito u ranim fazama bolesti. Tipični nalazi uključuju edem kosti koji je ujedno i prvi znak bolesti, a najčešće slijede osteolitičke ili sklerotične, a zatim hiperostozne koštane lezije, kao i periostalne i mekotkivne reakcije, ako postoje. Infektivni osteomijelitis i maligni tumori kostiju isključuju se biopsijom kosti (10,11).

Nesteroidni protuupalni lijekovi (NSAID) lijekovi su prve linije, sa zabilježenim stopama odgovora do 80 % (12). Oralni steroidi, metotreksat, sulfasalazin, kolhicin, bisfosfonati i inhibitori čimbenika tumorske nekroze alfa (TNF-α) mogu se upotrebljavati kao alternativna terapija u slučajevima u kojima bolesnici ne reagiraju na nesteroidne protuupalne lijekove ili tijekom pogoršanja u tijeku bolesti (egzacerbacija), te kako bi se spriječili recidivi. Protuupalno djelovanje azitromicina također može pridonijeti pozitivnom kliničkom terapijskom učinku (13). U ovom radu prikazujemo slučaj 13-godišnjeg dječaka koji je patio od bolova u lumbalnom dijelu kralježnice i kojemu je postavljena konačna dijagnoza KRMO-a u KBC-u Zagreb. Naš cilj je pridonijeti izbjegavanju pogrešnih dijagnoza i kasnog dijagnosticiranja ove bolesti.

PRIKAZ BOLESNIKA

Predstavljen nam je slučaj 13-godišnjeg dječaka koji od svoje 7. godine pati od bolova koji se projiciraju u lumbosakralni dio kralježnice. Bol je izazvana traumom koja se dogodila 2013. godine tijekom sata tjelesnog odgoja (TZK) (kolut naprijed). Što se tiče opće anamneze porođaj je prošao bez poteškoća, a APGAR ocjena pri rođenju bila je 9/10. Prije tog događaja dječak nije bolovao ni od kakve bolesti sve do svoje 7. godine. Bolesnik je 2013. godine hospitaliziran zbog bolova u lumbalnom dijelu kralježnice. Nakon što je je magnetskom rezonancijom (MR) otkriven minimalni diskontinuitet lijeve mase u lateralnom dijelu križne kosti u razini S1 bez značajnijeg pomaka uz prisutnost edema kosti, postavljena je sumnja na prijelom križne kosti (slika 1, 2A, 2B, 3). Bolesnik je otpušten iz bolnice s dijagnozom križobolje nepoznate etiologije te mu je propisana farmakološka terapija analgeticima i fizikalna terapija. Zbog prisutnosti blage boli koja nije napredovala do jake ili ograničavajuće razine, bolesnik je provodio fizikalnu terapiju jednom godišnje do 2017. kada mu je nakon općeg liječničkog pregleda postavljena dijagnoza skolioze. Tijekom tog razdoblja došlo je i do pogoršanja boli.

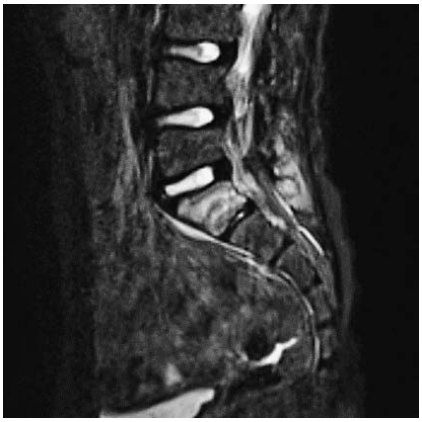

Figure 1 Lumbosacral MRI – STIR sagittal view
Slika 1. MR prikaz lumbosakralne kralježnice – sagitalni presjek u STIR-u
Caption / Opis slike: Bone and soft tissue oedema of S1, minimal discontinuation of the left mass of the lateral sacral bone in the level of S1 without significant displacement and with the presence of bone oedema. / Edem kosti i mekog tkiva u segmentu S1, minimalni diskontinuitet lijeve mase u lateralnom dijelu križne kosti u razini S1 bez značajnijeg pomaka uz prisutnost edema kosti.

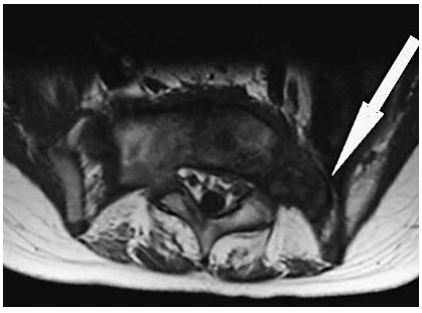

Figure 2A T2 MRI transversal view (S1)
Slika 2A. Transverzalni MR presjek na T2 mjerenoj slici (S1)
Caption / Opis slike: Hypointense signal in the left lateral mass of the sacral bone representing bone oedema. / Hipointenzivni signal u lijevoj lateralnoj masi križne kosti predstavlja edem kosti.

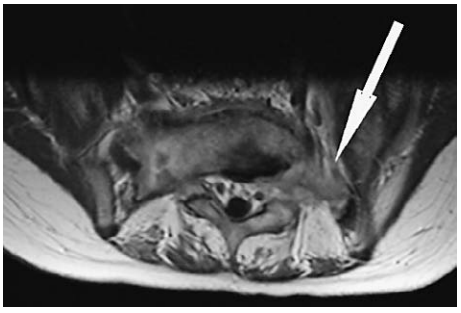

Figure 2B Postcontrast T1 MRI (S1)
Slika 2B. Postkontrastna T1-mjerena slika na MR presjeku
Caption / Opis slike: Postcontrast enhancement of the oedema. / Postkontrastno povećanje edema.

and enteral nutrition therapy. Shortly afterwards, while looking for a second opinion, the patient was taken in by another department and processed by an orthopaedic surgeon and a paediatric rheumatologist. At that

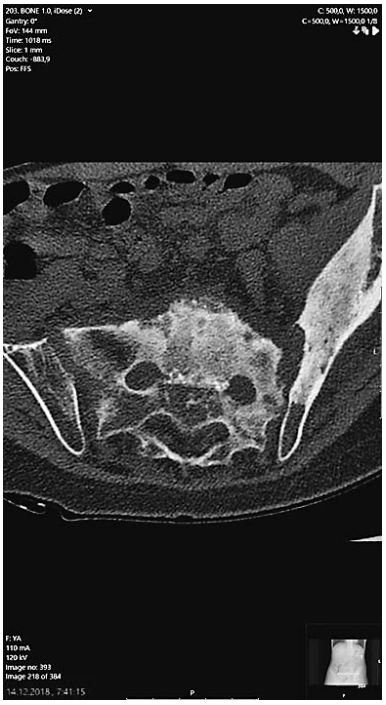

Figure 3 MSCT scan, axillary view (Dec 14, 2018)
Slika 3. MSCT snimka, aksilarni presjek (14. prosinca 2018.)
Caption / Opis slike: Sclerosis of the affected bone (sacral bone, iliac bone, vertebral body). / Skleroza zahvaćene kosti (križna kost, ilijakalna kost, trup kralješka).

Nakon pet godina dječak je hospitaliziran zbog anemije i pothranjenosti te je nakon kraćeg razdoblja otpušten iz bolnice uz preporuku uzimanja željeza i primjenu enteralne nadomjesne terapije. Ubrzo nakon toga, a tijekom traženja drugog mišljenja, bolesnik je primljen na drugi odjel na kojem su ga u sklopu obrade pregledali ortoped i pedijatrijski reumatolog. Tada su bolesniku napravljene sve standardne imunološke pretrage koje su bile negativne. Komponenta komplementa C4 bila je normalna kao i ukupna aktivnost komplementa, ali je otkriveno blago povećanje komponente C3. Uz to, inicijalne vrijednosti upalnih parametara bile su povišene 2018. godine (sedimentacija eritrocita (SE) 80/1 sat, C-reaktivni protein (CRP) 48 mg/L, fibrinogen 5,6 g/L), nije uočena leukocitoza (L 8,67 [1e9]/ L).

U rujnu 2018. godine napravljena je kontrolna magnetska rezonancija koja je otkrila značajnu progresiju bolesti od 2013. godine. Otkrivene su zone visokog intenziteta signala u metodama mjerene snimke magnetske rezonancije (na *engl. Turbo Inversion Recovery Magnitude*, TIRM) i T2 tehnike snimanja trupa kralješaka L5, S1, S2 i S3 sa znakovima signala visokog intenziteta koji se protežu od peteljke luka kralješka L5 do spinoznog nastavka. Također su prisutni znakovi regionalnog edema mekog tkiva i edematozne promjene masnog tkiva u prednjem dijelu unutar lumbalno-sakralnog dijela spinalnog kanala. Uz to, uočeni su znakovi destrukcije kosti prednjeg segmenta L1 trupa kralješka. Preporučeno je učiniti biopsiju. Nalaz scintigrafije kostiju iz studenoga 2018. pokazao je vrlo intenzivnu koštanu remodelaciju i izražen vaskularni prostor u križnoj kosti i zdjelici u lijevom dijelu. Na CT-u iz pro-

time, the patient underwent all standard immunological tests, which were all negative. The complement component C4 was normal as was the total complement activity, but there was a slight elevation in the C3 component. Moreover, the initial inflammatory parameters were elevated in 2018 (Erythrocyte sedimentation rate (ESR) 80/1h, C-reactive protein (CRP) 48 mg/L, fibrinogen 5.6 g/L), no leucocytosis was observed (L 8.67 [1e9]/L).

In September 2018, a control MRI was made which showed significant progression of the disease since 2013. Zones of high intensity signal in turbo inversion recovery magnitude (TIRM) and T2 techniques of vertebral bodies L5, S1, S2 and S3 were found with signs of high intensity signals extending from the pedicle of vertebral arch of the L5 vertebral body to the spinous process. There were also signs of regional oedema of the soft tissue and oedematous changes of the anterior adipose tissue inside the lumbar and sacral region of the spinal canal. Moreover, signs of bone destruction of the ventral segment of the L1 vertebral body were observed. Biopsy was recommended. Bone scintigraphy findings from November 2018 showed very intensive bone remodeling and expressed vascular space in the sacral bone and pelvis on the left side. On the CT scan from December 2018 changes of bone structure of the L5 vertebral body, the sacral bone (mainly S1, S2 and S3 vertebral bodies, more notable to the paramedian left) and the wings of the iliac bone on the left side were depicted. Furthermore, the inhomogeneous and reduced bone structure of the mentioned part of the skeleton with erosive, osteolytic and osteoblastic changes was shown, in addition to the fragmentation of the bone in the region of the left sacroiliac joint. These changes were also present at the cranial segment of the right sacroiliac joint (SI) joint with pseudo-enlargement at the cranial parts of both SI joints. The enlarged wing of the iliac bone with sclerotic and lytic lesions was found (Figure 4). Changes in the adipose tissue were also described, mainly around the mentioned part of the skeleton and in the region of the neural foramen from the L5 to the S1 segment and sacral foramen of the S1 segment on the left side. Irregular curves of the anterior cortex of the sacral bone from the S1 to the S3 vertebral body, along with the adipose tissue changes and a small portion of liquid in the anterior sacral region were also described. Given all of these pathological findings, the patient was diagnosed with chronic active osteomyelitis and referred to a rheumatologist and an orthopaedic surgeon for consultation.

In January 2019, the patient was admitted at the UHC Zagreb, the Department of Orthopaedic Surgery. At that time, the patient did not experience severe pain. Nothing significant was found in the patient's clinical status, except for the low body mass index (BMI) (14.4 kg/m^2). In terms of his locomotor status,

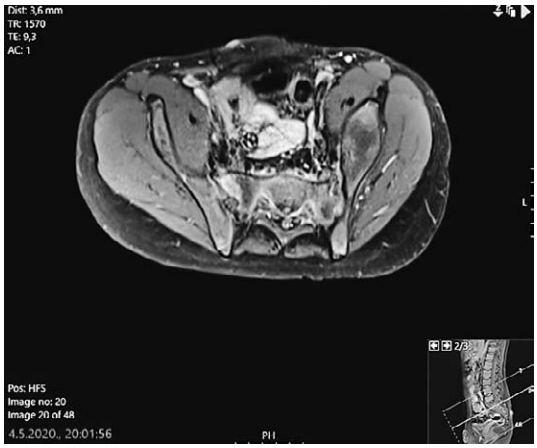

Figure 4 Control finding of postcontrast T1 FS MRI (May 4, 2020)

Slika 4. Kontrolni nalaz postkontrastne T1 F -mjerene slike na MR presjeku (4. svibnja 2020.)

Caption / Opis slike: Unchanged mass on the left side of the affected vertebra. / Nepromijenjena lijeva masa na zahvaćenom kralješku.

sinca 2018. utvrđene su promjene koštane strukture trupa kralješka L5, križne kosti (uglavnom trupa kralješaka S1, S2 i S3, izraženije paramedijalno lijevo) i krila ilijačne kosti s lijeve strane. Nadalje, prikazana je nehomogena i oslabljena koštana struktura navedenog dijela skeleta s erozivnim, osteolitičkim i osteoblastičnim promjenama, te fragmentacijom kosti u predjelu lijevog sakroilijakalnog zgloba. Te su promjene bile prisutne i na kranijalnom segmentu desnog sakroilijakalnog zgloba (SI) s pseudo-povećanjem na kranijalnim dijelovima oba SI zgloba. Nađeno je povećano krilo ilijakalne kosti sa sklerotičnom i litičkom lezijom iste (slika 4). Opisane su i promjene u masnom tkivu, uglavnom oko navedenog dijela skeleta te u području neuralnog foramena od segmenta L5 do S1 i sakralnog foramena S1 s lijeve strane. Također su opisane nepravilne krivulje prednjeg korteksa križne kosti od trupa kralježaka S1 do S3 uz promjene masnog tkiva i mali udio tekućine u prednjoj sakralnoj regiji. S obzirom na sve patološke nalaze, bolesniku je dijagnosticiran kronični aktivni osteomijelitis te je upućen na pregled kod svojeg reumatologa i ortopeda.

U siječnju 2019. bolesnik je primljen na Odjel za ortopedske operacije KBC-a Zagreb. U to vrijeme bolesnik nije osjećao jaku bol. Ništa značajno nije nađeno u kliničkom statusu bolesnika, osim niskog indeksa tjelesne mase (BMI) (14,4 kg/m2). Što se tiče motoričkog statusa dječak je pokazao smetnje prilikom savijanja prema naprijed. Na Thomayerovom testu (vrši prstiju-pod u saginjanju prema naprijed) izmjerena je udaljenost od 41 cm, na Schoberovom testu izmjereno je 1,5 cm, Mennellov klinički test za sakroilijakalne zglobove bio je negativan, test distrakcije zdjelice bio je negativan, Gowersov znak bio je pozitivan, sagitalni profil kralježnice bio je u razini, a Lasègue (ispružena

the boy showed perturbations when performing repeated forward bending tasks, Thomayer's test (fingertips-floor in forward bending) value was 41 cm, Schober's test value was 1.5 cm, Mennell's clinical test for sacroiliac joints was negative, sacroiliac distraction test was negative, Gowers' sign was positive, the sagittal profile of the spine was at level, and the Lasègue's (straight-leg) test showed no irritation on either side of the spinal roots. However, the left leg was 1.5 cm shorter and finally, the shortened and tense tendons of the hamstrings on both sides were found. The human leukocyte antigen (HLA) test was positive for HLA B27, while the interferon-gamma release assay (IGRA) was negative. The patient was indicated for bone biopsy. After histopathologic findings of the bone tissue, which showed reactive changes in the bone marrow with newly-formed connective tissue, the final diagnosis of CRMO of the pelvis and spine with a positive HLA B 27 result has been established. The patient was monitored by a paediatric rheumatologist and following therapy with indomethacin and bisphosphonate, the pain subsided. Bisphosphonate therapy was initiated in September 2020, and a maximal dose was administered throughout treatment. Shortly after that, the treatment was continued with NSAIDs. The patient responded well to bisphosphonate therapy and not only did he experience less pain, but this also resulted in a reduction of the inflammation parameters, an improvement of the patient's general condition, and an improvement of the patient's locomotor status and his clinical findings. Finally, at that time, the complications of CRMO such as pathological fractures and neurologic deficits were prevented.

At a follow-up examination in September 2021, a pelvis MRI without and with contrast was performed. In comparison with the previous MRI examination, this did not show significant changes in the distribution and the extent of the previously described bone lesions in the area of the lower lumbar segments, sacral bone, and pelvic bones. The urinary bladder, soft tissue and pelvic structures show normal morphology and signal intensity. There was no enlargement of the lymph nodes in the scanned area with normal large blood vessels. There was no free fluid in the pelvis, but there was still minimal effusion in the left coxofemoral joint.

In April 2022, a clinical and radiological worsening of the findings had occurred. The patient started to experience morning stiffness. After the examination, the diagnosis of juvenile spondyloarthritis on the base of CRMO was established. In addition to that, vitiligo was diagnosed by a paediatric dermatologist shorty after. Considering the stated facts, biological therapy was indicated, and from May 2022 treatment with Humira (adalimumab) was initiated. The most recent control MRI done in March 2023 showed a significant improvement in the radiological findings which was the

noga) test nije pokazao iritaciju spinalnih korijena ni na jednoj strani. Međutim, lijeva noga je bila 1,5 cm kraća i konačno su utvrđene skraćene i napete tetive koljena s obje strane. Test humanog leukocitnog antigena (na engl. *human leukocyte antigen*, HLA) pokazao je pozitivan HLA B27, dok je test oslobađanja interferona gama (na engl. *interferon-gamma release assay*, IGRA) bio negativan. Indicirana mu je biopsija kosti. Nakon patohistoloških nalaza koštanog tkiva, koji su pokazali reaktivne promjene u koštanoj srži s novonastalim vezivnim tkivom, postavljena je konačna dijagnoza KRMO-a zdjelice i kralježnice s pozitivnim HLA B 27. Bolesnik je bio pod praćenjem pedijatrijskog reumatologa, a nakon terapije indometacinom i bisfosfonatima, bolovi su bili manje izraženi. Terapija bisfosfonatima uvedena je u rujnu 2020, a primijenjena je maksimalna doza lijeka. Ubrzo nakon toga nastavljeno je liječenje nesteroidnim protuupalnim lijekovima (NSAID). Bolesnik je dobro podnosio terapiju bisfosfonatima, a osim smanjenja boli došlo je i do smanjenja upalnih parametara, poboljšanja općeg stanja, a poboljšao se i njegov motorički status i klinička slika. Tada su konačno spriječene komplikacije KRMO-a poput patoloških prijeloma i neuroloških deficita.

Na kontrolnom pregledu u rujnu 2021. učinjena je magnetska rezonancija zdjelice bez kontrasta i s kontrastom. U usporedbi s prethodnom magnetskom rezonancijom (MR), nisu utvrđene značajne promjene u distribuciji i opsegu prethodno opisanih koštanih lezija u području donjih lumbalnih segmenata, križne kosti i kostiju zdjelice. Mokraćni mjehur, meko tkivo i strukture zdjelice pokazuju normalnu morfologiju i intenzitet signala. Nije bilo povećanja limfnih čvorova u snimljenom području s normalnim velikim krvnim žilama. Nije bilo slobodne tekućine u zdjelici, ali bio je prisutan minimalan izljev u lijevom koksofemoralnom zglobu.

U travnju 2022. došlo je do kliničkog i radiološkog pogoršanja nalaza. Bolesnik je počeo osjećati jutarnju ukočenost. Nakon pregleda postavljena je dijagnoza juvenilnog spondiloartritisa na temelju KRMO-a. Nedugo nakon toga pedijatrijski dermatolog postavio je dijagnozu vitiliga. S obzirom na navedeno, bolesniku je indicirana biološka terapija te je u svibnju 2022. godine započeto liječenje Humirom (adalimumab). Posljednja kontrolna magnetska rezonancija učinjena u ožujku 2023. godine pokazala je značajno poboljšanje radioloških nalaza koji su se vratili u prijašnje stanje, te poboljšanje kliničke slike i smanjenje navedenih simptoma.

RASPRAVA

KRMO je rijetka bolest koja se često pogrešno ili kasno dijagnosticira. Zbog suptilnog početka simptoma, razdoblja djelomične remisije i pogoršanja bolesti

same as before, followed by an improvement in the clinical findings and a reduction of the mentioned symptoms.

DISCUSSION

CRMO is a rare disease which happens to be often misdiagnosed or diagnosed at a late stage. With its subtle onset of symptoms, periods of partial remission and exacerbation and an unclear etiology and pathophysiology, CRMO presents complications in diagnosis. Sites that are most often involved include the metaphysis of the long bones, the clavicles, and the vertebral bodies. According to Guariento et al., most commonly the vertebral bodies of the thoracic spine are involved (58%) with sclerosis and endplate abnormality present in 13% of cases (14). The mandible, pelvis, and small bones of the hands and feet, can also be involved (8). Furthermore, Stojkic et al. reported a case of an adolescent male patient who presented with recurrent swelling of the temporal region of skull as a uncommon clinical presentation of CRMO (15). In our patient, lumbosacral vertebral bodies and pelvis were affected. Generally, CRMO presents with unspecific symptoms, laboratory and X-ray findings. Laboratory findings often show slightly elevated inflammatory parameters. Roderick et al. reported in their study that CRP findings were slightly elevated in 14 out of 28 patients and ESR was raised in 16 out of 19 patients (10). Our patient had elevated inflammatory parameters during exacerbation periods. The golden standard for diagnosis is MRI. Indeed, in the case of our patient, the suspicion of an unconventional diagnosis was made after an MRI scan. However, CRMO still remains a diagnosis of exclusion. The diagnosis is most often established based on a combination of clinical, radiological and histological exams in addition to symptoms and clinical signs (16). Jansson et al. suggested the diagnostic criteria which included two major criteria or one major and three minor criteria, with the major ones being: radiologically proven osteolytic/-sclerotic bone lesion, multifocal bone lesions, palmoplantar pustulosis or psoriasis, sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis and the minor being: normal blood count and good general state of health, CRP and ESR mildly-to-moderately elevated, observation time longer than 6 months, hyperostosis, associated with other autoimmune diseases apart from palmoplantar pustulosis or psoriasis, grade I or II relatives with autoimmune or autoinflammatory disease, or with NBO (17). Bristol diagnostic criteria for CRMO use similar combination of criteria (10). Infectious osteomyelitis, malignancy (osteosarcoma, Ewing's sarcoma, leukemia, non-Hodgkin lymphoma), benign bone lesion (such as osteoid osteoma) and Langerhans cells histiocytosis (LCH) are the most common differential diagnoses (9). In addite još nepoznate etiologije i patofiziologije, kompliciranо je dijagnosticirati KRMO. Područja koja su najčešće zahvaćena su metafize dugih kostiju, ključne kosti i trupovi kralješaka. Prema Guarientu i sur. najčešće su zahvaćeni trupovi kralješaka torakalne kralježnice (58 %) sa sklerozom i abnormalnostima pokrovne plohe prisutnima u 13 % slučajeva (14). Mogu biti zahvaćena i područja poput donje čeljusti, zdjelice i malih kostiju šaka i stopala (8). Nadalje, u studiji koju su proveli Stojkić i dr. navodi se slučaj adolescentnog bolesnika koji je imao rekurentno oticanje temporalne regije lubanje kao neuobičajenu kliničku sliku KRMO-a (15). Kod našeg bolesnika bili su zahvaćeni lumbosakralni trupovi kralješaka i zdjelica. KRMO se općenito manifestira nespecifičnim simptomima, laboratorijskim i rendgenskim nalazima. Laboratorijski nalazi često pokazuju blago povišene vrijednosti upalnih parametara. U studiji koju su proveli Roderick i sur. navodi se da su nalazi CRP-a bili blago povišeni u 14 od 28 bolesnika, a SE je bila povišena u 16 od 19 bolesnika (10). Naš je bolesnik imao povišene vrijednosti upalnih parametara tijekom razdoblja pogoršanja bolesti (egzacerbacije). Zlatni standard za postavljanje dijagnoze je magnetska rezonancija (MR). Kod našeg bolesnika počelo se sumnjati na nekonvencionalnu dijagnozu nakon magnetske rezonancije (MR). Međutim, KRMO je i dalje dijagnoza isključenja. Dijagnoza se najčešće postavlja na temelju kombinacije kliničkih, radioloških i histoloških pretraga zajedno sa simptomima i kliničkim znakovima (16). U studiji koju su proveli Jansson i sur. predloženi su dijagnostički kriteriji s dva glavna kriterija ili jednim glavnim i tri sporedna kriterija od kojih su glavni: radiološki dokazana osteolitička/sklerotična koštana lezija, multifokalne koštane lezije, palmoplantarna pustuloza ili psorijaza, sterilna biopsija kosti sa znakovima upale i/ili fibroze i skleroza te sporedni kriteriji koji su: normalna krvna slika i dobro opće zdravstveno stanje, CRP i SE blago do umjereno povišeni, vrijeme praćenja duže od 6 mjeseci, hiperostoza, povezana s drugim autoimunim bolestima osim palmoplantarne pustuloze ili psorijaze, srodnici u prvom ili drugom koljenu s autoimunom ili autoinflamatornom bolešću, ili s nebakterijskim osteomijelitis (17). Bristolski dijagnostički kriteriji za KRMO imaju sličnu kombinaciju kriterija (10). Infektivni osteomijelitis, maligne bolesti (osteosarkom, Ewingov sarkom, leukemija, ne-Hodgkinov limfom), benigne koštane lezije (kao što je osteoidni osteom) i histiocitoza Langerhansovih stanica (na engl. *Langerhans cells histiocytosis*, LCH) najčešće su diferencijalne dijagnoze (9). Uz to, zabilježene su sličnosti s juvenilnim spondiloartritisom, to jest, otkriveno je da postoji mogućnost da jedna bolest evoluira u drugu (3). Ova zabilježena evolucija bolesti dogodila se u slučaju našeg bolesnika kojem je dijagnosticiran juvenilni spondiloartritis na

tion to that, similarities with juvenile spondyloarthritis were reported, moreover the fact that the evolution from one disease to another is not impossible (3). This reported evolution occurred in the case of our patient, who was diagnosed with juvenile spondyloarthritis on the base of CRMO after he started experiencing morning stiffness. NSAIDs are the first-line therapy, with reported response rates of up to 80% (12). Oral steroids, methotrexate, sulphasalazine, colchicine, bisphosphonates and TNF-α blockers can be used as an alternative treatment in cases in which the patients are unresponsive to NSAIDs, during exacerbations and in order to prevent relapses. Furthermore, Hug et al. reported the role of paediatric spine surgery interventions in patients with spine involvement with the aim of preventing disease complications such as neurological deficits, pain, deformity or instability, although there are no current guidelines for such management (18). Our patient responded well to the treatment with a combination of indomethacin and bisphosphonates, but eventually, due to the worsening of symptoms, radiological findings and the evolution of juvenile spondyloarthritis on the base of CRMO, biological therapy was indicated. After the treatment with adalimumab, there was an improvement of both clinical and radiological findings in the case of our patient.

In a child with chronic and recurrent bone pain, elevated inflammatory parameters, osteolytic and osteosclerotic lesions found on X-ray, long-lasting bone oedema found on MRI on multiple sites and excluded infectious or malignant etiology, CRMO should always be suspected. Proper diagnosis improves the quality of life for children in multiple ways. Most notably, it puts an end to an incorrect, difficult and prolonged antibiotic therapy and frequent exposure to radiation (by recurrent X-ray and CT imaging). Another significant benefit of applying the right treatment is the reduction of symptoms as well as avoidance of complications from CRMO, like bone damage and bone deformities. Frequent MRI controls and early HLA typing are suggested for the purpose of avoiding misdiagnoses. Moreover, bone oedema on radiological findings, if present, should indicate a possible rheumatic and immunological origin of the condition. We hope that this case report will prove to be helpful in in establishing a proper diagnosis and treatment of patients with CRMO and we look forward to new studies about this rare and serious disease.

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temelju KRMO-a nakon što je počeo osjećati jutarnju ukočenost. Nesteroidni protuupalni lijekovi (NSAID) lijekovi su prve linije, sa zabilježenim stopama odgovora do 80 % (12). Oralni steroidi, metotreksat, sulfasalazin, kolhicin, bisfosfonati i blokatori TNF-α mogu se upotrebljavati kao alternativna terapija u slučajevima u kojima bolesnici ne reagiraju na nesteroidne protuupalne lijekove ili tijekom pogoršanja u tijeku bolesti (egzacerbacija), te kako bi se spriječili recidivi. Nadalje, u studiji koju su proveli Hug i sur. navodi se uloga kirurških intervencija kralježnice u pedijatrijskih bolesnika sa zahvaćenom kralježnicom u svrhu sprječavanja komplikacija bolesti kao što su neurološki deficiti, bol, deformacija ili nestabilnost, iako trenutno ne postoje smjernice za takvu vrstu liječenja (18). Naš je bolesnik dobro reagirao na liječenje kombinacijom indometacina i bisfosfonata, ali mu je na kraju, zbog pogoršanja simptoma, radiološkog nalaza i evolucije juvenilnog spondiloartritisa na temelju KRMO-a, indicirana biološka terapija. Nakon liječenja adalimumabom došlo je do poboljšanja kliničkog i radiološkog nalaza našeg bolesnika.

Na KRMO treba uvijek posumnjati u djeteta s kroničnim i ponavljajućim bolovima u kostima, povišenjem upalnih parametara, osteolitičkim i sklerotičkim lezijama na rentgenskoj (RTG) snimci, uz vidljivi dugotrajni koštani edem na raznim područjima na magnetskoj rezonanciji i isključenom infektivnom ili malignom etiologijom. Pravilna dijagnoza višestruko poboljšava kvalitetu života djece. Što je najbitnije, omogućuje prekid nepravilne, teške i dugotrajne terapije antibioticima i učestalog izlaganja zračenju (ponovnim rendgenskim i CT snimanjima). Još jedna značajna prednost primjene odgovarajuće terapije je smanjenje simptoma kao i izbjegavanje komplikacija KRMO-a, poput oštećenja i deformacije kostiju. Predlažu se česte kontrole magnetske rezonancije i rana tipizacija tkiva (HLA) kako bi se izbjegle pogrešne dijagnoze. Nadalje, edem kosti na radiološkim nalazima, ako je prisutan, trebao bi ukazivati na moguće reumatološko i imunološko podrijetlo bolesti. Nadamo se da će ovaj prikaz slučaja pomoći u dijagnosticiranju i liječenju bolesnika s KRMO-om i pozdravljamo nove studije o ovoj rijetkoj, ali teškoj bolesti.

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