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CASE REPORT PRIKAZ BOLESNIKA

PAPA SYNDROME – DIAGNOSTIC AND THERAPEUTIC PATH FROM PAEDIATRIC TO ADULT RHEUMATOLOGIST

PAPA SINDROM – DIJAGNOSTIČKI I TERAPIJSKI PUT OD PEDIJATRIJSKOG DO ADULTNOG REUMATOLOGA

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Abstract

PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum and Acne) is an autosomal dominant, hereditary autoinflammatory disease resulting from mutations in the PSTPIP1/CD2BP1 gene on chromosome 15q. The disease begins in childhood, most often from the age of 2 to 11, and it is characterised by a triad of symptoms: pyogenic (sterile) arthritis, pyoderma gangrenosum and acne. The disease usually begins with arthritis and is rarely recognised in the initial stage. The appearance of skin symptoms of the disease, either acne or pyoderma gangrenosum, along with the previously existing arthritis, should arouse suspicion of the existence of PAPA syndrome and direct doctors to perform further genetic testing. The triad of symptoms does not always have to be present, but the presence of two of the three symptoms with a confirmed gene mutation is a sufficient criterion for the diagnosis of the disease. Biological drugs have shown the greatest effectiveness in treatment, and IL1 inhibitors or TNF alpha inhibitors are most often used medications. In later life, the joint manifestations gradually calm down, but the skin manifestations can last for many years with frequent relapses and remissions even with applied therapy, which makes this syndrome a great challenge for the treatment of this disease. Considering the small number of cases with PAPA syndrome described in the literature, we present to you an interesting case of a twenty-five-year-old patient with this disease and his challenging diagnostic and therapeutic path from childhood to adulthood.

Key words: autoinflammatory disorder, PAPA syndrome, pyogenic arthritis, pyoderma gangrenosum, acne, biological drugs

Sažetak

PAPA sindrom (piogeni artritis, *pyoderma gangrenosum* i akne) je autosomno dominantna, nasljedna autoinflamatorna bolest koja je posljedica mutacije gena PSTPIP1/CD2BP1 na kromosomu 15q. Bolest najčešće počinje u djetinjstvu, od druge do jedanaeste godine života, a karakterizira ju trijas simptoma: piogeni (sterilni) artritis, *pyoderma gangrenosum* i akne. Bolest obično počinje artritisom i rijetko se prepoznaje u ranim fazama bolesti. Pojava kožnih simptoma bolesti, bilo akni ili *pyoderma gangrenosum*, uz prethodno postojeći artritis, trebala bi pobuditi sumnju na postojanje PAPA sindroma te uputiti liječnike na daljnje genetsko testiranje. Trijas simptoma ne mora uvijek biti prisutan, ali postojanje dva od tri simptoma uz potvrđenu mutaciju gena dovoljan je kriterij za dijagnozu bolesti. Naj-

veću učinkovitost u liječenju pokazali su biološki lijekovi, a najčešće su korišteni inhibitori IL-1 i TNF alfa. U kasnijoj životnoj dobi zglobne se manifestacije postupno smiruju, ali kožne manifestacije mogu trajati godinama s čestim relapsima i remisijama čak i uz uključenu terapiju, što ovaj sindrom čini velikim izazovom za liječenje. S obzirom na mali broj slučajeva s PAPA sindromom opisanih u literaturi, predstavljamo Vam zanimljiv slučaj dvadesetpetogodišnjeg bolesnika s ovom bolešću i njegov zahtjevan dijagnostički i terapijski put od djetinjstva do odrasle dobi.

Ključne riječi: autoinflamatorni poremećaj, PAPA sindrom, piogeni artritis, pyoderma gangrenosum, akne, biološki lijekovi

INTRODUCTION

PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum and Acne) is a rare autoinflammatory disease which is inherited in an autosomal dominant fashion through mutations in the PSTPIP1/CD2BP1 gene on chromosome 15q. These mutations produce a hyperphosphorylated PSTPIP1 protein and alter its involvement in the activation of the "inflammasome" involved in the production of interleukin-1β (IL-1β). Excessive production of IL-1β is a clear molecular characteristic of PAPA syndrome (1).

Autoinflammatory disease is similar to autoimmune diseases in its clinical characteristics, but they differ in the pathophysiological mechanism of the disease. In autoimmune diseases, antibodies are created against certain antigens in the body, and in autoinflammatory diseases, antibodies are not created, but in the field of genetic mutation, hyperphosphorylated proteins are produced that change its action in the activation of inflammasomes that are involved in the production of IL-1β. The autoinflammatory response occurs in several ways: unregulated production of cytokines by the inflammasome, intracellular stress, damage to regulatory pathways, increased NF-kappaB signalling, ubiquitination disorder, alteration of the interferon pathway, and complement activation. The emergence of new genetic analysis techniques and the discovery of genes involved in autoinflammatory diseases have enabled a better understanding of the basic innate immune pathways and pathogenetic mechanisms, thus creating new perspectives in targeted therapies. (2)

Two mutations were found in a protein called CD2-binding protein 1 (CD2BP1). This protein is part of the inflammatory pathway associated with other autoinflammatory syndromes such as: Familial Mediterranean fever (FMF), mevalonate kinase deficiency (hyperimmunoglobulin-D syndrome, HIDS), periodic fever syndrome, Muckle-Wells syndrome (MWS), multisystem inflammatory disease in neonates and familial cold autoinflammatory syndrome (FCAS). The exact mechanism of the manner in which the mutated gene causes the disease has not yet been established. (3)

In some cases, a person inherits a pathogenic variant from the parent who has the genetic disease. In other cases, the disease occurs due to a new pathogenic variant (de novo) in the causative gene and there is no fam-

UVOD

PAPA sindrom (piogeni artritis, *pyoderma gangrenosum* i akne) je rijetka autoinflamatorna bolest koja se nasljeđuje autosomno dominantno mutacijom gena PSTPIP1/CD2BP1 na kromosomu 15q. Ove mutacije proizvode hiperfosforilirani protein PSTPIP1 i mijenjaju njegovo sudjelovanje u aktivaciji „inflamasoma" uključenog u proizvodnju interleukina-1β (IL-1β). Prekomjerna proizvodnja IL-1β jasna je molekularna značajka PAPA sindroma (1).

Autoinflamatorna bolest je po svojim kliničkim karakteristikama slična autoimunim bolestima, ali se razlikuju u patofiziološkom mehanizmu nastanka bolesti. U autoimunim bolestima se stvaraju antitijela na određene antigene u organizmu, a kod autoinflamatornih bolesti ne stvaraju se antitijela, već se na terenu genetske mutacije proizvode hiperfosfolirilirani proteini koji mijenjaju njegovo djelovanje u aktivaciji inflamasoma koji su uključeni u proizvodnju IL-1β. Autoinflamatorni odgovor nastaje na više načina: neregulirano proizvodnjom citokina posredstvom inflamasoma, unutarstaničnim stresom, oštećenjem regulatornih putova, pojačanom NF-kappaB signalizacijom, poremećajem ubikvitinacije, izmjenom interferonskog puta i aktivacijom komplemenata. Pojava novih tehnika genetske analize i otkrića gena uključenih u autoinflamatorne bolesti omogućile su bolje razumijevanje osnovnih urođenih imunoloških putova i patogenetskih mehanizama, otvarajući tako nove perspektive u ciljanim terapijama. (2)

Dvije su mutacije pronađene u proteinu koji se zove CD2 vezni protein 1 (CD2BP1). Ovaj protein dio je upalnog puta povezanog s drugim autoinflamatornim sindromima kao što su: obiteljska mediteranska vrućica (engl. *familial Mediterranean fever* – FMF), manjak mevalonat kinaze (engl. *hyperimunoglobulin-D syndrome* – HIDS), sindrom periodične groznice, Muckle-Wellsov sindrom (MWS), multisistemska inflamatorna bolest novorođenčeta i obiteljski autoinflamatorni sindrom uzrokovan hladnoćom (engl. *familial cold autoinflammatory syndrome* – FCAS). Još uvijek nije utvrđen točan mehanizam kako mutirani gen uzrokuje bolest. (3)

U nekim slučajevima osoba nasljeđuje patogenu varijantu od roditelja koji ima genetsku bolest. U drugim slučajevima, bolest se javlja zbog nove patogene vari-

ily history of the disease. A child of a person with an autosomal dominant disease has a 50% (1 in 2) chance of inheriting the variant and the disease. Typically, children who inherit a dominant variant will have the disease, but they may be more or less affected than their parents. Sometimes a person can have a pathogenic variant of an autosomal dominant disease and show no signs or symptoms of the disease. (4)

CD2BP1, also known as proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1), is highly expressed in neutrophils. PSTPIP1 can form interactions with pyrin, a protein mutated in FMF. Mutations in PAPA syndrome result in hyperphosphorylation of the PSTPIP1 protein and change its participation in the activation of the "inflammasome". This gene mutation places PAPA syndrome in the same pathogenic pathway as FMF. (5,6)

These mutations were found both in PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum and acne) and in similar syndromes such as PASH (pyoderma gangrenosum, acne and hidradenitis suppurativa) or PAPASH (pyogenic arthritis, acne, pyoderma gangrenosum and hidradenitis suppurativa). (6)

The characteristic form of PAPA syndrome is the classic triad that includes florid and painful flares of recurrent sterile arthritis, pyoderma gangrenosum and severe cystic acne, although only 25% of patients will have all three manifestations. (5)

Sterile pyogenic arthritis begins in the first decade of life, affects one joint and is progressively destructive in nature. It most often affects the ankles, knees, elbows and wrists. Exploratory joint surgery in PAPA syndrome shows non-specific inflammation of the joint and hypertrophic synovitis with marked synovial thickening and a high number of leukocytes found in joint fluid aspiration. (7)

Pyoderma gangrenosum lesions are less common, although they are an important feature of PAPA syndrome. Initially, they are characterised by small superficial erythematous violaceous papules, which develop into sterile pustules and aggressive ulcerative skin lesions mainly visible on the extremities. Biopsy of pyoderma gangrenosum skin lesions shows a predominance of neutrophilic inflammatory infiltrate in the dermis.

Most patients develop acne, usually a form of nodulocystic acne, which generally appears after puberty and persists into adulthood. Nodulocystic acne can cause scarring if left untreated. Some characteristics of this syndrome include the decrease of arthritis intensity over time followed by the exacerbation of the skin manifestations. (6,7,8)

Fever, fatigue, oral ulceration, proteinuria, haematuria and keratitis have also been described in patients with PAPA syndrome. (7,8)

jante (*de novo*) u uzročnom genu i nema obiteljske povijesti bolesti. Svako dijete osobe s autosomno dominantnom bolešću ima 50% (1 od 2) šanse da naslijedi varijantu i bolest. Tipično, djeca koja naslijede dominantnu varijantu imat će bolest, ali mogu biti manje ili više pogođena od svojih roditelja. Ponekad osoba može imati patogenu varijantu autosomno dominantne bolesti i ne pokazivati znakove ili simptome bolesti. (4)

CD2BP1, također poznat kao protein 1 u interakciji s prolin-serin-treonin fosfatazom (PSTPIP1), visoko je izražen u neutrofilima. PSTPIP1 može stvarati interakcije s pirinom, proteinom mutiranim u FMF. Mutacije u PAPA sindromu rezultiraju hiperfosforilacijom PSTPIP1 proteina i mijenjaju njegovo sudjelovanje u aktivaciji inflamasoma. Ova mutacija gena smješta PAPA sindrom na isti patogeni put kao FMF. (5,6)

Ove mutacije su nađene kako u PAPA sindromu (piogeni artritis, p*yoderma gangrenosum* i akne) tako i u njemu sličnim sindromima kakvi su PASH (*pyoderma gangrenosum*, akne i supurativni hidradenitis) ili PAPASH (piogeni artritis, akne, *pyoderma gangrenosum* i supurativni hidradenitis). (6)

Karakterističan oblik PAPA sindroma jest klasična trijada koja uključuje bujne i bolne napade rekurentnoga sterilnog artritisa, *pyodermu gangrenosum* i teške cistične akne, iako će samo 25% bolesnika imati izražene sve tri manifestacije. (5)

Sterilni piogeni artritis počinje u prvom desetljeću života, zahvaća jedan zglob i progresivno-destruktivne je prirode. Najčešće zahvaća gležnjeve, koljena, laktove i zapešća. Eksploratorna kirurgija zglobova u PAPA sindromu pokazuje nespecifičnu inflamaciju zgloba i hipertrofični sinovitis s izraženim sinovijalnim zadebljanjem i visokim brojem leukocita u aspiratu zgloba. (7)

Lezije *pyoderma gangrenosum* rjeđe su, iako su važna značajka PAPA sindroma. U početku su karakterizirane malim površinskim eritematoznim violaceoznim papulama, koje se razvijaju u sterilne pustule i agresivne ulcerativne kožne lezije koje se uglavnom vide na ekstremitetima. Biopsija kožnih lezija *pyoderma gangrenosum* pokazuje dominaciju neutrofilnoga upalnog infiltrata u dermisu.

Većina pacijenata razvije akne, obično nodulocistične forme, koje se općenito pojavljuju nakon puberteta i traju u odrasloj dobi. Nodulocistične akne mogu uzrokovati ožiljke ako se ne liječe. Ono što je karakteristično za sindrom jest da s vremenom intenzitet artritisa opada, a dolazi do pogoršanja kožnih promjena. (6,7,8)

Vrućica, umor, oralne ulceracije, proteinurija, hematurija, keratitis također su opisani u slučajevima bolesnika s PAPA sindromom. (7,8)

Pored kliničkih znakova bolesti za potvrdu dijagnoze je neophodno genetsko testiranje i dokazivanje prisutnosti mutacije na XV kromosomu gena PSTPIP1/CD2BP1, i to je temelj za potvrdu dijagnoze PAPA sindroma. (4,7,8)

In addition to the clinical signs of the disease, genetic testing and evidence of the presence of a mutation on the chromosome 15 of the PSTPIP1/CD2BP1 gene is necessary to confirm the diagnosis, and this is the basis for confirming the diagnosis of PAPA syndrome. (4,7,8)

Considering the small number of described cases of PAPA syndrome in the world, the therapeutic approach to these patients is still insufficiently researched. Nonsteroidal anti-inflammatory drugs did not show a significant effect, except for pain relief. Systemic corticosteroids, some DMARDs (Disease Modifying Antirheumatic Drugs) have shown their effectiveness in treatment, and recently biological drugs have become the drugs of choice, primarily TNF-alpha inhibitors (Tumour Necrosis Factor Alpha) and interleukin-1 inhibitors. Topical or intralesional corticosteroids are considered the first line of local therapy and can be applied to the active border of the ulcer. Topical calcineurin inhibitors such as topical tacrolimus are considered first-line therapy and have been used to treat pyoderma gangrenosum in several cases. (9,10,11,12)

CASE REPORT

In the case of our patient, who is now 25 years old, the first symptoms of the disease appeared in the second year of life with elevated body temperature and swelling and pain in the knees. The family history was negative for autoimmune diseases. This patient's disease was originally thought of as infectious arthritis and he was treated for a year with different antibiotics administered orally and parenterally, with non-steroidal anti-inflammatory drugs, but this did not yield and significant results. When the patient reached the age of three, a diagnosis of juvenile idiopathic arthritis was made, and methotrexate was introduced into the therapy. Until the age of seven, the patient intermittently experienced the phases of exacerbation and remission of the disease. Exacerbations of symptoms occurred spontaneously and could not be linked to changes in lifestyle or exposure to environmental factors. In terms of clinical symptoms, swelling of the knees, elbows and ankles were the ones that occurred during that period. On several occasions, the patient's joints were punctured, and intra-articular glucocorticoids were administered during therapy, which led to a short-term improvement in the patient's condition. The disease was accompanied by increased inflammatory reactants, leukocytosis with a predominance of neutrophil granulocytes and anaemia. Immunological tests, including rheumatic tests and antinuclear antibodies, were negative. The HLA-B27 locus was not present. At the age of 10, the patient was introduced to etanercept therapy, which was administered to him during the course of

S obzirom na mali broj opisanih slučajeva PAPA sindroma u svijetu, terapijski pristup ovim bolesnicima još uvijek je nedovoljno istražen. Nesteroidni antiinflamatorni lijekovi nisu pokazali značajan učinak, osim ublažavanja boli. U liječenju su svoju učinkovitost pokazali sistemski kortikosteroidi, neki DMARD-ovi (engl. *Disease Modifying Antirheumatic Drugs*), a u novije vrijeme biološki lijekovi postaju lijekovi izbora, prvenstveno inhibitori TNF-alfa (engl. *Tumor Necrosis Factor Alpha*) i inhibitori interleukina-1. Lokalni ili intralezijski kortikosteroidi smatraju se prvom linijom lokalne terapije i mogu se primijeniti na aktivnu granicu ulkusa. Lokalni inhibitori kalcineurina kao što je lokalni takrolimus smatraju se terapijom prve linije i korišteni su za liječenje *pyoderma gangrenosum* u nekoliko slučajeva. (9,10,11,12)

PRIKAZ BOLESNIKA

U bolesnika, koji sada ima 25 godina, prvi simptomi bolesti javili su se u drugoj godini života povišenom tjelesnom temperaturom te oteklinama i bolovima u koljenima. Obiteljska anamneza negativna na autoimune bolesti. Izvorno je shvaćen kao infektivni artritis i liječen godinu dana različitim antibioticima *per os* i parenteralno, nesteroidnim antireumaticima, ali bez značajnijeg uspjeha. U dobi od tri godine postavljena je dijagnoza juvenilnoga idiopatskog artritisa te je u terapiju uveden metotreksat. Do sedme godine života bolesnik intermitentno ulazi u faze egzacerbacije i remisije bolesti. Egzacerbacije simptoma pojavljivale su se spontano i nisu se mogle dovesti u vezu s promjenama stila života ili izloženošću čimbenicima okoline. Klinički su se u tom razdoblju javljale otekline koljena, laktova i gležnjeva. U nekoliko navrata punktirani su zglobovi i ordinirani intraartikularno glukokortikoidi, što je dovodilo do kratkotrajnog poboljšanja stanja bolesnika. Bolest je bila praćena povišenim upalnim reaktantima, leukocitozom s predominacijom neutrofilnih granulocita i anemičnim sindromom. Imunološki testovi uključujući reumatske testove i antinuklearna antitijela bili su negativni. HLA-B27 lokus nije bio prisutan. U dobi od deset godina bolesniku se uvodi u terapiju etanercept koji je primao oko godinu dana, ali bez terapijskog odgovora. U tom razdoblju kod bolesnika se počinju javljati kožne promjene, učinjena je biopsija kože koja je pokazala upalni neutrofilni infiltrat, ali se patolog tada nije izjasnio o konkretnoj dijagnozi. Promjene na koži s vremenom se pogoršavaju. U dvanaestoj godini života kod bolesnika se pojavljuju akne, što se pripisuje pubertetu. Terapija metotreksatom nastavljena je do dvanaeste godine života, kada zbog egzacerbacije bolesti i neadekvatnoga terapijskog odgovora liječnici odlučuju uključiti infliksimab. Kod bolesnika dolazi do djelomičnog poboljšanja i povlačenja simptoma, no tijekom primjene pete doze lijeka

one year, but no significant therapeutic response was achieved during this time. During that period, the patient started to notice the appearance of skin changes, and following that a skin biopsy was performed, which showed an inflammatory neutrophilic infiltrate, but the pathologist did not make a specific diagnosis at that time. The skin changes worsened over time. At the age of 12, the patient developed acne, which was attributed to puberty. Methotrexate therapy was continued until the age of 12, when the patient's doctors decided to include infliximab in the therapy due to exacerbation of the disease and inadequate therapeutic response. The patient experienced partial improvement and withdrawal of symptoms, but during the administration of the fifth dose of the drug, a severe allergic reaction in the form of angioedema developed, and the drug was discontinued. After the washout period, adalimumab was included in the therapy, which was administered to the patient during the course of the following two years. After that, the patient and his family changed their place of residence, and the treatment was continued in another clinical centre. During the first examination by a paediatric rheumatologist in our clinical centre, based on the clinical features and the course of the disease, PAPA syndrome was suspected, and a skin biopsy was requested once again, which, according to the pathologist's description, corresponded to pyoderma gangrenosum and could be differentially diagnosed as PAPA syndrome. Figures 1, 2, 3 and 4 show some clinical and radiographic features of the patient, which are consistent with the diagnosis of PAPA syndrome: a deformed right elbow, with atrophic scars after surgery, narrowing of the intra-articular space visible on X-ray, joint remodelling and effusion, pyoderma gangrenosum on the volar side of the forearm and nodulocystic acne on the face.

Genetic testing was indicated, and the blood was sent for analysis to the Department of Genetics at the Paediatric Hospital "Bambino Gesu" in Italy, and the existence of a pathological mutation of the PSTPIP1 gene, heterozygous on chromosome 15, substitution E748G<C in exon 11, which is a known mutation for PAPA syndrome, was proven. Then the biological drug adalimumab, during the administration of which the patient did not achieve a complete remission of the disease, was replaced by an inhibitor of interleukin-1, the drug called anakinra. After a month and a half of using the aforementioned drug (1 x 100 mg SC), there was a significant improvement in the skin manifestations, but in the laboratory findings there was a sudden increase in the values of liver transaminases, aspartate aminotransferase (AST) 115 (ref. values in the range of 0–31 U/L), alanine aminotransferase (ALT) 204 (ref. value in the range of 0–36 U/L) and increased alkaline phosphatase (ALP) 235 (ref. value in the range of

razvija se teška alergijska reakcija u vidu angioedema te se lijek prekida. Nakon „*wash out*" razdoblja u terapiju se uključuje adalimumab koji prima sljedeće dvije godine. Nakon toga bolesnik i njegova obitelj mijenjaju mjesto stanovanja i sele se iz jednoga kliničkog centra u drugi radi medicinske skrbi. Prilikom prvog pregleda pedijatrijskog reumatologa u našem kliničkom centru, na temelju kliničke slike i tijeka bolesti postavlja se sumnja na PAPA sindrom, te se ponovno traži biopsija kože, što prema opisu patologa odgovara *pyoderma gangrenosum* i može se diferencijalno dijagnostički uklopiti u PAPA sindrom. Na slikama 1, 2, 3 i 4 prikazana su neka klinička i radiografska obilježja u bolesnika, sukladna PAPA sindromu, deformirani desni lakat s ožiljnim atrofičnim promjenama kože nakon operativnog zahvata, radiografski vidljivo suženje intraarti-

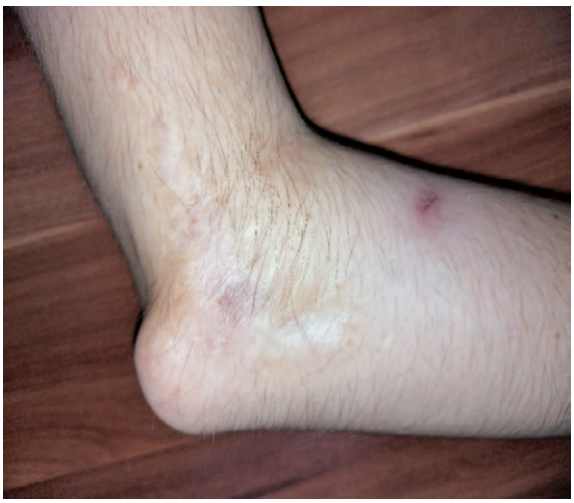

Figure 1 Deformed right elbow with atrophic scars after surgery

Slika 1. Deformirani desni lakat, s ožiljnim atrofičnim promjenama kože nakon operativnog zahvata

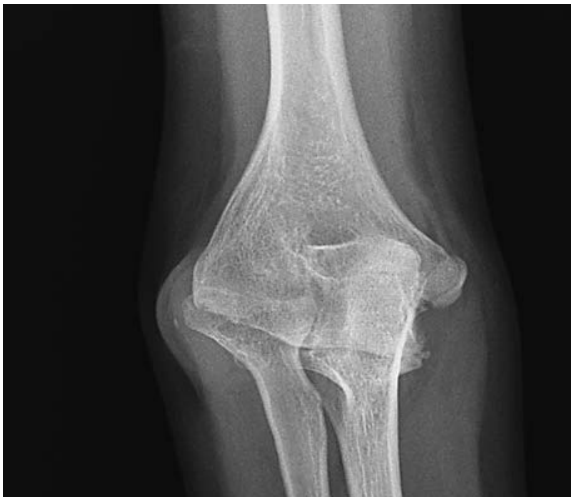

Figure 2 X-ray of the elbow joint, with visible narrowing of the intra-articular space with joint remodelling and effusion

Slika 2. Radiološka slika lakatnog zgloba, s vidljivim suženjem intraartikularnog prostora, remodeliranjem zglobnih površina i izljevom

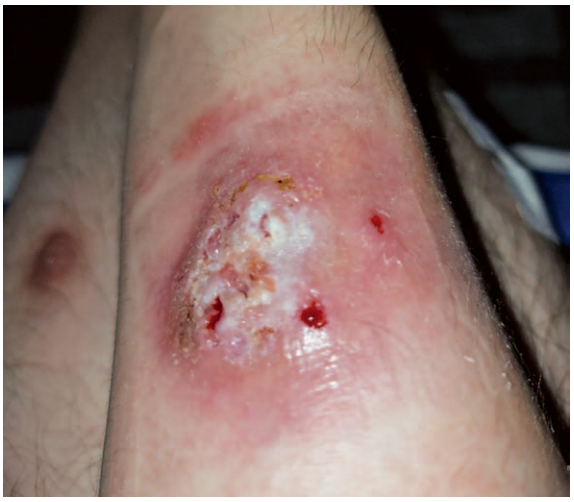

Figure 3 Pyoderma gangrenosum on the volar side of the forearm
Slika 3. Pyoderma gangrenosum na volarnoj strani podlaktice

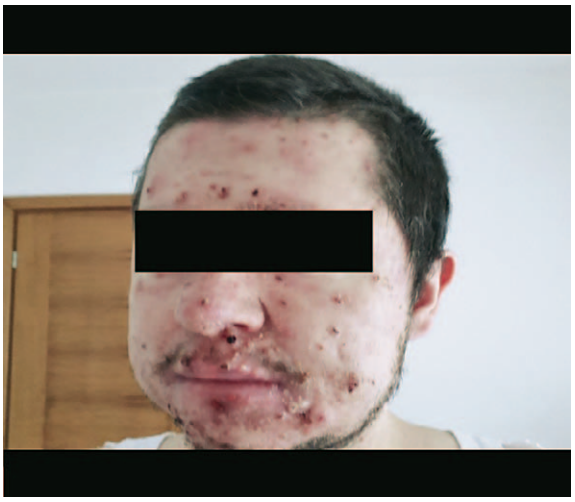

Figure 4 Facial nodulocystic acne
Slika 4. Nodulocistične akne na licu

0–100 U/L). For this reason, the administration of the mentioned biological drug was suspended. Given that the level of transaminases did not decrease even after discontinuing the medication, the patient was referred for gastroenterohepatological treatment, where acute hepatitis B was confirmed after performing clinical tests (HBV DNA PCR – 456,413 copies/ml). The patient was not previously vaccinated against hepatitis B, but the markers for hepatitis B and C were regularly controlled according to the protocol before the inclusion of DMARDs and biological therapy, which were negative in the earlier period. In addition to that, as part of the gastroenterohepatological treatment, an immunological treatment was performed to rule out the development of autoimmune hepatitis, which was negative (antimitochondrial antibodies, AMA: neg., anti-smooth muscle antibodies ASMA: neg., liver kidney microsome type 1 antibodies, LKM1: neg., anti-liver cytosol 1 autoantibody, LC1: neg., anti-soluble-liver-antigen autoantibodies, anti-SLA: neg). In the following period, according to the recommendation of the gastroenterologist, all immunosuppressive therapy was discontinued and the antiviral drug Entacavir was included in the therapy, in a dose of 0.5 mg per day. During this period, the patient turned 18 and was referred to an adult rheumatologist for the continuation of his treatment. Several years of struggle with ailments for which we had no possibility of adequate treatment due to active hepatitis B followed. NSAIDs meant to be administered orally and parenterally, topical NSAIDs for joint pain and glucocorticoid creams for skin changes were prescribed.

In 2019, the patient started using isotretinoin in a dose of 3 x 10 mg, which led to a short-term improvement in his condition with acne, but in the long term

kularnog prostora, remodeliranje zglobnih površina i izljev u području, *pyoderma gangrenosum* na volarnoj strani podlaktice i nodulocistične akne na licu.

Indicirano je genetičko testiranje, te se krv pošalje na analizu na Odjel za genetiku pri Pedijatrijskoj bolnici „Bambino Gesu“ u Italiji, te je dokazano postojanje patološke mutacije PSTPIP1 gena heterozigot na XV kromosomu, supstitucija E748G<C u egzonu 11, što je poznata mutacija za PAPA sindrom. Tada je biološki lijek adalimumab, na koji bolesnik nije imao potpunu remisiju bolesti, zamijenjen inhibitorom interleukina 1, lijekom anakinra. Nakon mjesec i pol primjene navedenog lijeka (1 x 100 mg s.c.) nastupilo je značajno poboljšanje kožnih manifestacija, ali u laboratorijskim nalazima dolazi do iznenadnog porasta vrijednosti jetrenih transaminaza, aspartat aminotransferaze (AST) 115 (ref 0–31 U/L), alanin aminotransferaze (ALT) 204 (ref 0–36 U/L) te porasta vrijednosti alkalne fosfataze (ALP) 235 (ref 0–100 U/L). Zbog toga je obustavljena primjena navedenog biološkog lijeka. S obzirom na to da niti nakon prekida primjene lijeka nije došlo do sniženja nivoa transaminaza, bolesnik je upućen na gastroenterohepatološku obradu, gdje je nakon kliničkih pretraga verificiran akutni hepatitis B (HBV DNA PCR – 456 413 kopija/ml). Bolesnik prethodno nije bio cijepljen protiv hepatitisa B, ali su redovito kontroliani markeri na hepatitis B i C prema protokolu prije uključivanja DMARD-a i biološke terapije, koji su u ranijem razdoblju bili negativni. Također, u sklopu gastroenterohepatološke obrade učini se i imunološka obrada radi isključivanja razvoja autoimunog hepatitisa, koja je negativna (antimitohondrijska antitijela – AMA – neg., antitijela na glatku muskulaturu – ASMA – neg., antitijela na mikrosome jetre i bubrega – LKM1 – neg., antitijela usmjerena protiv jetrenog citosolnog proteina 1 – LC1 – neg., antitijela na topljivi jetreni antigen – anti SLA

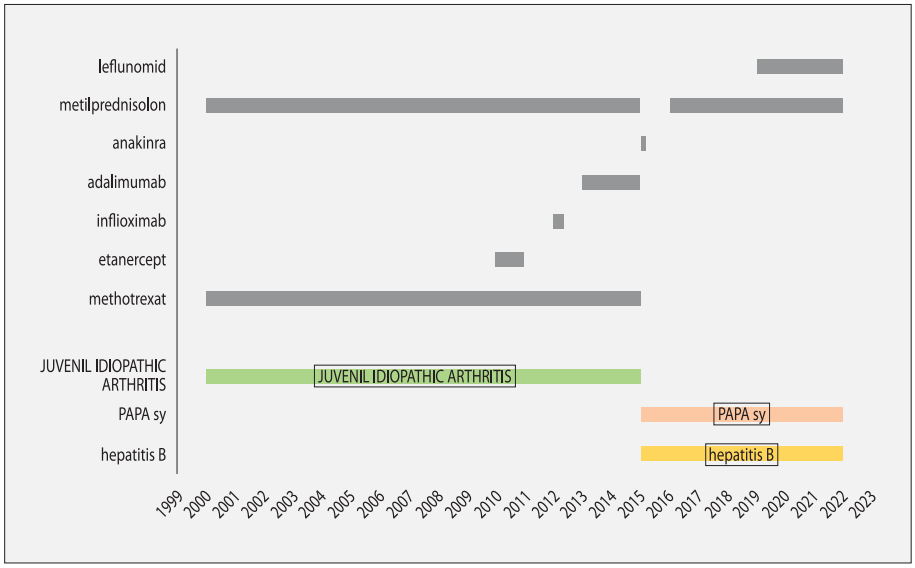

FIGURE 5 Graphic representation of prescribed therapy and diagnoses since 1999 until 2023
SLIKA 5. Grafički prikaz ordinirane terapije i dijagnoze od 1999. do 2023. godine

the drug did not show a significant therapeutic effect, and it was discontinued. After the negative result of the HBV PCR test, a glucocorticoid, methylprednisolone, was reintroduced into the patient's therapy in a minimal dose: at first it was administered at a dose of 8 mg per day, then 4 mg per day, while leflunomide tablets were also included in the therapy in a dose of 20 mg per day. Over time, the joint manifestations went into partial remission, but the skin changes remained in the stage of relapse, significantly impairing the patient's quality of life and increasing the tendency to develop secondary infections. The chronology of the drugs used, and the leading diagnoses are shown in a graphic representation in Figure 5. After three negative HBV DNA PCR tests and completed antiviral therapy, the patient was prepared for the inclusion of biological therapy with the drug called canakinumab, which we expect to show an adequate therapeutic effect.

DISCUSSION

PAPA syndrome is an extremely rare disease, and to confirm the diagnosis, we need genetic testing and confirmation of the presence of a pathological mutation on the chromosome 15 along with corresponding clinical features. The disease most often begins with arthritis, and in the initial phase, due to the presence of pus in the joint, a bacterial infection is suspected, and patients are wrongly treated with antibiotics along with possible punctures and drainage of the joints. Unnecessary use of antibiotics and joint puncture may cause psychological and physical trauma to a child who has been misdiagnosed for many years. If an autoimmune disease is suspected, most often such cases are diagnosed as juvenile idiopathic arthritis. The absence of skin changes in the first stage of the disease is the reason due to which the correct diagnosis is not made in

– neg.). U sljedećem razdoblju, prema preporuci gastroenterologa, isključena je sva imunosupresivna terapija i uključen je antivirusni lijek entacavir, 0,5 mg dnevno. U tom razdoblju bolesnik navršava 18 godina i prelazi na liječenje adultnom reumatologu. Uslijedilo je nekoliko godina borbe s tegobama za koje nismo imali mogućnosti adekvatnog liječenja zbog aktivnog hepatitisa B. Propisivani su nesteroidni antireumatici *per os* i parenteralno, topikalni nesteroidni antireumatici za bolne zglobove i glukokortikoidne kreme za kožne promjene.

U 2019. godini bolesnik je počeo koristiti izotretinoin 3 x 10 mg, što je dovelo do kratkotrajnog poboljšanja stanja s aknama, ali dugoročno lijek nije pokazao značajan terapijski učinak te je njegova primjena obustavljena. Nakon negativnog nalaza HBV PCR testa, u terapiju bolesnika ponovno je uveden glukokortikoid – metilprednizolon u minimalnoj dozi, najprije 8 mg dnevno, potom 4 mg dnevno, dok je uključen i leflunomid tbl. 20 mg dnevno. S vremenom zglobne manifestacije prelaze u djelomičnu remisiju, ali kožne promjene su u stadiju relapsa te značajno narušavaju kvalitetu života bolesnika i povećavaju sklonost razvoju sekundarnih infekcija. Kronologija korištenih lijekova i vodeće dijagnoze prikazane su grafički na slici 5. Nakon tri negativna HBV DNA PCR testa i završene antivirusne terapije, bolesnik je pripremljen za uključivanje biološke terapije lijekom kanakinumab, za koji očekujemo da će pokazati adekvatan terapijski učinak.

RASPRAVA

PAPA sindrom je izuzetno rijetka bolest, a za potvrdu dijagnoze neophodno je genetičko testiranje i potvrda prisutnosti patološke mutacije na XV kromosomu uz odgovarajuću kliničku sliku. Bolest najčešće započinje artritisom te se u početnoj fazi s obzirom na prisutnost „gnojnog" sadržaja u zglobu posumnja na

time. With the appearance of skin changes, primarily pyoderma gangrenosum, PAPA syndrome can be suspected because acne itself is usually associated with puberty. All patients with elements of pyogenic sterile arthritis and the appearance of skin changes, whether it be acne or pyoderma gangrenosum, should undergo genetic testing. The presence of other skin changes such as hidradenitis suppurativa in addition to acne and arthritis should lead us in the direction of PASHA syndrome or another entity from the group of autoinflammatory diseases. If the diagnosis of PAPA syndrome is confirmed, considering how destructive this disease can be to the joints and the skin, the treatment should be started with drugs that have shown the best effectiveness so far, namely interleukin-1 inhibitors or TNF-alpha inhibitors. The application of the IL-1β inhibitor, anakinra, primarily has a good effect on calming the inflammatory process in the joint, and remissions of skin changes have been proven after its application in some cases. If anakinra does not give an adequate therapeutic response, which is also recorded in the literature, the use of canakinumab is recommended, which has shown a better therapeutic effect on skin changes. Maintaining skin hygiene also plays a huge role in the treatment. Sterile wound dressing is necessary, because wounds can be the site of infection, either bacterial or viral. Given that we excluded other mechanisms of disease transmission, we believe that skin defects in our patient are responsible for hepatitis B virus infection. The use of topical glucocorticoids in the form of creams can show a short-term effect, but due to the effect on the skin itself, long-term use should be avoided. In addition to that, the use of systemic glucocorticoids should be considered only in cases of acute disease. Changes on the visible parts of the skin, and disease exhaustion have a great psychological impact on the patient, and it is necessary to provide such patients with psychological support. Often, these patients decide against having children because they are aware that this is a genetic disease. Deformities that occur on large joints as part of this syndrome sometimes require surgical correction in order to maintain the functionality of the joint or endoprosthetic replacement. Considering the different cases described in the literature, each patient with this syndrome requires an individual approach and lifelong adjustment of therapy.

CONCLUSION

PAPA syndrome is a complex entity, which we should keep in mind in terms of differential diagnosis, because cases of this disease occur sporadically in our climate, and remain undiagnosed for a long time. The disease is of a chronic nature, and after the diagnosis, the applied therapy sometimes does not yield success-

bakterijski infekt i bolesnici se pogrešno tretiraju antibioticima uz eventualne punkcije i drenažu zglobova. Nepotrebna primjena antibiotika te punkcija zglobova uzrokuju psihičku i fizičku traumu za dijete koje se vodi pod pogrešnom dijagnozom dugi niz godina. Ako se i posumnja na autoimunosnu bolest najčešće se ovakvi slučajevi vode pod dijagnozom juvenilnog idiopatskog artritisa. Nedostatak kožnih promjena u prvoj fazi bolesti jest razlog zašto se na vrijeme ne postavi prava dijagnoza. Kod pojave kožnih promjena, prvenstveno *pyoderma gangrenosum*, može se posumnjati na PAPA sindrom jer se same akne obično povezuju s pubertetskim periodom. Svi bolesnici s elementima piogenog sterilnog artritisa i pojavom kožnih promjena, bilo da se radi o aknama ili o *pyoderma gangrenosum*, trebali bi biti podvrgnuti genetskom testiranju. Prisutnost drugih kožnih promjena tipa *hidroadenitis supurtiva* uz akne i artritis treba nas voditi u pravcu PASH sindroma ili nekog drugog entiteta iz skupine autoinflamatoronih bolesti. Ako se potvrdi dijagnoza PAPA sindroma, s obzirom na destruktivnost same bolesti kako na zglobove tako i na kožu liječenje bi se trebalo započeti lijekovima koji su do sada pokazali najbolju učinkovitost, a to su inhibitori interleukina-1 ili inhibitori TNF-alfa. Primjena inhibitora IL-1β – anakinre ima prvenstveno dobro djelovanje na smirivanje upalnog procesa na zglobu, a dokazane su i remisije kožnih promjena na njezinu primjenu u pojedinim slučajevima. Ako anakinra ne daje odgovarajući terapijski odgovor, što je također zabilježeno u literaturi, preporučuje se primjena kanakinumaba, koji je pokazao bolji terapijiski učinak na kožne promjene. Veliku ulogu u tretmanu ima i higijensko održavanje promjena na koži. Neophodno je sterilno previjanje, jer rane mogu biti mjesto ulaska infekta, bilo bakterijskog ili virusnog. Budući da smo isključili ostale mehanizme prijenosa bolesti, smatramo da su defekti na koži kod našeg bolesnika odgovorni za infekciju virusom hepatitisa B. Primjena lokalnih glukokortikoida u obliku krema može pokazati kratkoročni efekt, ali zbog samog učinka na kožu dugoročna primjena trebala bi se izbjegavati. Također, primjena sistemskih glukokortikoida treba se razmatrati samo u slučajevima akutizacije bolesti. Promjene na vidljivim dijelovima kože te iscrpljenost bolešću imaju velik psihološki utjecaj na bolesnika te je takvim bolesnicima neophodno pružiti i psihološku podršku. Često se ovakvi bolesnici zbog saznanja da se radi o genetskoj bolesti ne odlučuju imati djecu. Deformiteti koji nastanu u sklopu ovog sindroma na velikim zglobovima katkada zahtijevaju kiruršku korekciju radi održavanja funkcionalnosti zgloba ili ugradnju endoproteza. S obzirom na različite slučajeve opisane u literaturi, svaki bolesnik s ovim sindromom zahtijeva individualni pristup i doživotno prilagođavanje terapije.

ful therapeutic results. Comorbidities that may appear complicate the situation and make the treatment of these patients more difficult.

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ZAKLJUČAK

PAPA sindrom je složeni entitet, koji nam diferencijalno dijagnostički treba biti na umu, jer se u našem podneblju sporadično javljaju slučajevi te bolesti koji dugo vremena ostaju nedijagnosticirani. Bolest je kroničnog karaktera i terapija koja se uključi nakon postavljanja dijagnoze ponekad neće dati terapijske rezultate. Komorbiditeti koji se mogu pojaviti kompliciraju situaciju i otežavaju liječenje tih bolesnika.

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