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Prikaz slučaja
Case report
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DESTRUKTIVNA STAFILOKOKNA PLEUROPNEUMONIJA KOD DVOGODIŠNJEG DEČAKA SA HIPERIMUNOGLOBULIN-E SINDROMOM

DESTRUCTIVE STAPHYLOCOCCAL PLEUROPNEUMONIA IN A TWO-YEAR-OLD BOY WITH HYPERIMMUNOGLOBULIN-E SYNDROME

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Sažetak - Hiperimunoglobulin-E sindrom (HIES) je retka, teška imunodeficijencija koja se karakteriše povišenim serumskim koncentracijama IgE, eozinofilijom i teškim, ponavljanim bakterijskim i gljivičnim infekcijama. Prisutna je loša regulacija imunološkog sistema sa smanjenom produkcijom citokina, naročito interferona i smanjena produkcija specifičnih antitela na invazivne bakterije čija kapsula sadrži polisaharidne antigene. Opisane su i skeletne malformacije koje se mogu protumačiti prekomernom produkcijom interleukina-4 koji dovodi do patološke resorpcije koštanog tkiva. Zbog deficita imunološkog sistema i malformacija koštanog i vezivnog tkiva HIES predstavlja multisistemski poremećaj. Dugoročna prognoza nije poznata. Prikazujemo bolesnika koji je od najranijeg uzrasta imao recidivne bakterijske infekcije, a krajem druge godine života tešku destruktivnu stafilocoknu pleuropneumoniju sa formiranjem pneumotocela i pneumotoraksom. Bolesnika karakterišu dismorfija lica i skeletne anomalije koje su najizraženije na kranijalnom delu lobanje. Dijagnoza HIES je postavljena na osnovu povišenih vrednosti serumskog IgE, hipereozinofilije, kao i nalaza oslabljene funkcije leukocita *in vivo* i *in vitro*. Analiza rodoslovnog stabla porodice našeg bolesnika ukazuje na autozomno-dominantni tip nasleđivanja HIES.

Cljučne reči: Jobov sindrom; Predškolsko dete; Imunološke bolesti; Pleuropneumonija; Stafilocokna pneumonija

Summary - Hyperimmunoglobulin-E syndrome (HIES) is a rare immunodeficiency disorder that is characterized by elevated serum concentration of IgE, eosinophilia and severe, recurrent bacterial and fungal infections. Poor regulation of immune system is evident, with decreased production of cytokines, especially interferon. Production of specific antibodies to capsular polysaccharide antigens is decreased. Skeletal malformations have been reported in these patients. They can be caused by excessive production of interleukin-4, which may lead to pathologic bony tissue resorption. Due to immune system deficiency and malformations of skeletal and connective tissue, HIES is a multisystem disorder. We present a patient with recurrent bacterial infections since the early age. At the age of two years he presented with severe destructive staphylococcal pneumonia with pleural effusion, pneumatocele formation and pneumothorax. The patient also had a dysmorphic face and skeletal malformations that were most evident at the head. The diagnosis of HIES was made on the basis of elevated serum concentrations of IgE, hypereosinophily, and decreased leukocyte function *in vivo* and *in vitro*. Family history of our patient showed an autosomal-dominant inheritance pattern of HIES.

Key words: Job's Syndrome; Child, Preschool; Immunologic Diseases; Pleuropneumonia; Pneumonia, Staphylococcal

Uvod

Hiperimunoglobulin-E sindrom (HIES) je retka imunodeficijencija koju karakterišu rekurentni stafilocokni apscesi kože i potkožnog tkiva, stafilocokne pneumonije sa razvojem pneumotocela, kao i izrazito visoka serumska koncentracija imunoglobulina E [1,2]. HIES su prvi put prikazali 1966. godine Davis i saradnici [3]. Do danas je opisano više od 200 slučajeva HIES, a u našoj zemlji pet bolesnika [4,5]. Povećana sklonost ka infekcijama uzrokovana je poremećajima imunološkog sistema, ali patogenetski mehanizmi nisu u potpunosti razjašnjeni. HIES odlikuju i poremećaji koji nisu vezani za imunološki sistem, a odnose se na skeletne anomalije koje se raznoliko ispoljavaju [4].

Rekurentni apscesi kože, potkožnog tkiva i limfnih čvorova mogu biti hladni, bez znakova lokalne inflamacije ili je prisutna izrazita gnojna reakcija. Česti su i apscesi pluća, kao i gnojne infekcije uva i sinusa. Najčešći uzročnici infekcija kod bolesnika sa HIES su *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pneumoniae* ili

Introduction

Hyperimmunoglobulin-E syndrome (HIES) is a rare immunodeficiency disorder that is characterized by recurrent skin abscesses, staphylococcal pneumonia with pneumatocele formation, as well as extremely elevated serum concentrations of immunoglobulin E [1,2]. HIES was first reported in 1966 by Davis et al. [3]. More than 200 cases of HIES were reported so far, and there are five patients in our country [4,5]. Immune system disorder makes these patients prone to infections, but the pathogenesis mechanisms are poorly understood. HIES is also characterized by disorders that are not associated with the immune system and are manifested as various skeletal malformations [4].

Recurrent abscesses of the skin, subdermal tissue and lymph nodes may be "cold", without evidence of local inflammation, or they can present with purulent reaction. Lung abscesses are also frequent, as well as purulent ear and sinus infections. These infections are most frequently caused by

Skraćenice

HIES - Hyperimmunoglobulin-E syndrome
 IL - interleukin
 Ig - imunoglobulin

Streptococcus grupe A. Nisu retke ni sistemske gljivične infekcije uzrokovane gljivicama iz rodova *Candida* i *Aspergillus*. Najteža komplikacija ponavljanih pneumonija kod bolesnika sa HIES je pojava pneumotocela koje se mogu sekundarno inficirati sa *Pseudomonas aeruginosa* i *Aspergillus spp.* [6].

Prikaz slučaja

U Institutu za zdravstvenu zaštitu dece i omladine u Novom Sadu u dva navrata je hospitalizovan bolesnik (u uzrastu od 14 i 21 mesec) zbog teških rekurentnih bakterijskih infekcija, kada je sprovedeno ispitivanje zbog sumnje na imunodeficijenciju.

Pri prvoj hospitalizaciji u našem Institutu, decembra 2002. godine, dečak je bio uzrasta 14 meseci. Iz anamneznihi podataka se vidi da bolesnik od drugog meseca života pati od čestih respiratornih infekcija a u jednom navratu, u četvrtom mesecu života, imao je jednu epizodu supurativnog otitisa kada je lečen ambulantno. U uzrastu od pet meseci, nakon primene treće doze DiTePer vakcine, na



Slika 1. Karakteristike lica kod pacijenta
 Fig. 1. Facial characteristics of a patient

Abbreviations

HIES - Hyperimmunoglobulin-E syndrome
 IL - interleukin
 Ig - immunoglobulin

Staphylococcus aureus, *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Streptococcus group A*. Patients with HIES are also prone to systemic fungal infections caused by *Candida* and *Aspergillus* species. The most severe complication of recurrent pneumonia in patients with HIES is pneumatocele formation that can be infected with *Pseudomonas aeruginosa* and *Aspergillus* species [6].

Case report

We report on a child that was twice admitted to the Institute of Children and Youth Health Care in Novi Sad, due to severe recurrent bacterial infections. Immunodeficiency was suspected and all necessary investigations have been done.

At first hospitalization in December 2002, the patient was 14 months of age. He had frequent respiratory infections since the age of two months, and at the age of four months he had an episode of suppurative otitis, when he was treated ambulatory. At the age of five months, parents noticed redness, swelling and necrotic changes at the DiTePer inoculation site. Fever developed and the infant was admitted to the Institute of Mother and Child Health Care "Dr. Vukan Čupić" where streptococcal sepsis was diagnosed and necrectomy was performed. After the age of eight months, the infant had recurrent episodes of suppurative otitis once a month. Due to a complication (mastoiditis), shortly before the patient was first admitted to our Institute, a bilateral mastectomy was performed at the Otorinolaryngology Clinic in Novi Sad.



Slika 2. Ožiljak nakon nekrektomije
 Fig. 2. Scarring after necrectomy

mestu aplikacije vakcine razvio se opsežan otok, crvenilo i nekroza, uz visoku febrilnost. Dete je hospitalizovano u Institutu za zdravstvenu zaštitu majke i deteta Srbije "Dr Vukan Čupić" gde je konstatovana streptokokna sepsa i urađena nekrektomija. Od osmog meseca života slede recidivi supurativnog otitisa jedanput mesečno i tada je dete hospitalno lečeno u subotičkoj bolnici. Zbog komplikacije u vidu mastoiditisa, neposredno pre prve hospitalizacije u našem Institutu, urađena je obostrana mastoidektomija na Klinici za otorinolaringologiju Kliničkog centra u Novom Sadu.

U porodičnoj anamnezi stric pati od furunkuloze i ima sličan oblik glave sa naglašenim čelom kao bolesnik. Serumski koncentracija IgE kod strica iznosi 523,2 IU/mL (do 52 IU/mL). Otac boluje od polenske astme, i ima povećan alarni dijametar, a serumski nivo IgE iznosi 1 494,4 IU/mL. U široj porodici sa očeve strane više osoba ima alergiju na polen.

Pri prijemu muško dete uzrasta 14 meseci, očuvane svesti, afebrilno, TM 10 kg (10 perc.), TV 80 cm (75 perc.), OG 49,5 cm (iznad 97 perc.), glava diskranična (skafocefalija), visoko i ispupčeno čelo, oči duboko usađene, širok koren nosa, šire nosnice, hipertelorizam, epikantus, gotsko nepce i asimetrija lica (Slika 1). Prisutna je hiperelastičnost zglobova. Na levoj nadlaktici ožiljak duž cele cirkumferencije, a na podlaktici grub linearni ožiljak dužine 4 cm (mesto prethodne reakcije na DiTePer vakcinu) (Slika 2). Na koži poglavine, na licu i vratu ekcematoide promene sa lihenifikacijom i ekzorijacijama. U nosu mukozan sekret, ždrelo i tonzile hiperemični, sa slivanjem mukoznog sekreta niz zadnji zid ždrela. Oba uva prekrivena zavojem nakon izvršene mastoidektomije. Nad plućima auskultatorno ranoinspirijumski pukoti. Ostali nalazi su bili uredni.

Laboratorijske analize ukazuju na povišene vrednosti reaktanata akutne faze inflamacije: SE 50/105 mm/h, fibrinogen 9,0 g/L (ref. vr. 2 - 4 g/L), CRP 12 mg/L (ref. vr. 6 mg/L), Le $20 \times 10^9/L$, segm 0,44, limfo 0,49, eoz. 0,07, Er $4,23 \times 10^{12}/L$, Hgb 104 g/L, trombociti $560 \times 10^9/L$. U koprokulturi je izolovana *Candida spp.*, što ide u prilog činjenici da kod ovih bolesnika dolazi do lakše kolonizacije digestivnog trakta gljivicama. Funkcija fagocita: nitroblutetrazolijum test i test fagocitoze uredni, dok izostaje inflamatorni odgovor *in vivo* (Rebuck-test kožnog prozora) i *in vitro* (oslabljen je odgovor na tuberkulin pri testu transformacije limfocita). Imunoglobulini seruma IgA, IgM i IgG su bili u granicama normalnih vrednosti, a serumski IgE 1 326 IU/mL (normalno do 52 IU/mL). Imunofenotipizacijom dobijena je normalna vrednost ukupnih T-limfocita CD3 i subpopulacija CD4 i CD8, kao i vrednosti B-limfocita (CD19) i NK ćelija (CD 56). Kranioigram ukazuje na normalne koštane strukture, ali lošije modeliran frontalni deo lobanje.



Slika 3. Rtg snimak pluća - pleuropneumonija sa pneumatoceleloma

Fig. 3. Chest x-ray - pleuropneumonia with pneumatocele

The family history was remarkable. The patient's uncle has furunculosis and a similar shape of face with a prominent forehead, and his IgE serum concentrations are elevated - 523,2 IU/mL (less than 52 IU/mL). The patient's father has asthma, broad nasal bridge, and his IgE serum concentrations are also elevated - 1494.4 IU/mL. Some other family members also have atopic diseases.

On admittance: the boy aged 14 months, was conscious and afebrile, (weight 10 kg (10 perc.), height 80 cm (75 perc.), head circumference 49,5 cm (over 97 perc.), scaphocephalic head with high prominent forehead, deeply set eyes, broad nasal bridge, nasal tip, and interalar distance, hypertelorism, epicanthus, gothic palate and facial asymmetry (Fig. 1). Joint hyperelasticity is present. Along the circumference of the left upper arm there was a rough 4 cm long linear scar (the DTP vaccine inoculation site) (Fig. 2). On the skin of the head and neck eczematous changes were present with lichenification and excoriation. There was a mucous secretion in the nose and the pharynx and tonsils were hyperemic. His ears were bandaged after mastoidectomy. Other physical examination findings were normal.

Laboratory investigations revealed elevated levels of acute phase reactants of inflammation: ESR 50/105 mm/h, fibrinogen 9,0 g/L (ref. value 2,0 - 4,0 g/L), CRP 12 mg/L (ref. vr. 6 mg/L), leukocyte count $20,0 \times 10^9/L$ with 44% neutrophils, 49% lymphocytes, 7% eosinophils, erythrocyte count $4,23 \times 10^{12}/L$, hemoglobin 104 g/L, thrombocytes $560 \times 10^9/L$. *Candida* species were isolated from the stool culture which is in accordance with the fact that in these patients gastrointestinal tract is prone to fungal colonization. Phagocyte function: nitroblue tetrazolium test and phagocytosis test were normal, but inflammatory response *in vivo* (Rebuck test) and *in vitro* was absent (delayed response to purified protein derivate - PPD). Immunologic investigations

Tokom hospitalizacije nastavljena je parenteralna terapija antibioticima (imipenem, vankomicin, amikacin) koja je započeta na Klinici za otorinolaringologiju zbog gnojnog mastoiditisa (uzročnik nije potvrđen bakteriološkom analizom ali je klinička slika ukazivala na verovatnu stafilokoknu etiologiju). Crevna kandidijaza je lečena antimikotikom (nistatin). Dete je otpušteno kući sa dijagnozom *Immunodeficientia* (Hiper IgE sindrom) uz preporučenu prevenciju fucidinskom kiselinom (*Stanicid* sirupom) do zakazane kontrole. Prevencija je samoinicijativno prekinuta nakon mesec dana, a dete nije dovedeno na kontrolu.

Dečak se dobro osećao do uzrasta od 21 meseca, kada se tokom boravka na moru pojavila gnojna infekcija kože u predelu vrata. Kožne promene se šire uz pojavu bolnog otoka limfnih čvorova na vratu i povišene telesne temperature. Ambulantno je započeta terapija oralnim antibiotikom koja nije bila efikasna. Zbog febrilnosti, kašlja i otežanog disanja dečak je po drugi put hospitalizovan na našem Institutu.

Pri prijemu je dečak uzrasta 21 mesec, svestan, febrilan, adinamičan, izrazito bled, dispnoičan i tahikardan. U predelu vrata brojne pustule na eritematoznoj koži, uz uvećanje lokalnog limfnog čvora koji je promera 3 cm, tvrde konzistencije, bolan na dodir. Nad plućima desno perkutorna potmulost, a auskultatorno izrazito oslabljen disajni zvuk, uz retke kasnoinspiratorne pukote. Laboratorijski nalazi ukazuju na ubrzanu sedimentaciju eritrocita 84/125 mm/h, leukocitozu $24,7 \times 10^9/L$, neutrofili 0,70, eozinofili 0,13 (aps. br. $3211/mm^3$), limfociti 0,17, Er $4,4 \times 10^{12}/L$, Hgb 10^9 g/L, HTC 0,341, trombociti $407 \times 10^9/L$, CRP 197 mg/L, fibrinogen 6,7 g/L. IgE preko 2000 IU/mL.

Rendgenski snimak pluća: desno vidljiv pleuralni izliv do visine okrajka četvrtog rebra. U senci izliva i iznad njega vidljive cistične šupljine, bez jasnog tečnog sadržaja, tankih zidova, sa nejasnim crtežom plućnog parenhima između cističnih formacija. Na levom plućnom krilu diskretno pojačan intersticijalni plućni crtež (Slika 3). Nakon plasiranja torakalnog drena evakuisano 340 mililitara mutnog sadržaja iz koga je iskultivisan *Staphylococcus aureus*. Nakon prestanka torakalne drenaže nastupa pogoršanje, zbog razvoja pneumotoraksa sa delimičnim kolapsom desnog plućnog krila, što je utvrđeno radiološkim pretragama (rendgenskim snimkom i CT-om grudnog koša). Dren je ponovno plasiran a drenaža desnog hemitoraksa nastavljena je još narednih 16 dana, do potpune reekspanzije plućnog krila. Terapija je sprovedena antibioticima (vankomicin, zatim kloksacilin) i antimikotikom nistatinom. Dete se otpušta u dobrom opštem stanju, urednog fizičkog nalaza, sa preporukom da dobija kloksacilin radi antistafilokokne profilakse. Na poslednjoj kontroli, mesec dana posle otpusta, dete je bilo dobrog opšteg stanja, urednog fizičkog nalaza, bez kliničkih znakova infekcije.

also revealed normal serum IgA, IgM and IgG concentrations; IgE was increased - 1329 IU/mL (normal 0-52 IU/mL). Immunophenotype of the peripheral blood lymphocytes was normal. Craniogram showed normal bone structure with poorly modulated frontal region of the skull.

During hospitalization, the patient received parenteral antibiotic therapy (imipenem, vancomycin, amikacin) which was initiated at Otorinolaryngology Clinic because of purulent mastoiditis (clinical appearance suggested staphylococcal etiology, although the causative agent was not isolated). Gastrointestinal candidiasis was treated with antifungal drug (nystatin). The patient was dismissed from the hospital with the diagnosis: Immunodeficiency (Hyper IgE syndrome) and fucidin acid (*Stanicid*) was suggested until check-up. The parents discontinued the prevention a month later and did not bring the child for check-up.

The boy was doing well until the age of 21 months, when a purulent skin infection appeared on the neck. Skin lesions were spreading, with painful swelling of the lymph nodes on the neck and fever. Ambulatory treatment with oral antibiotics failed. The patient was once again admitted to our Institute due to cough, impaired breathing and fever.

On admittance: the boy was aged 21 months, conscious, febrile, adynamic, pale, dyspnoic and tachycardic. Neck: numerous pustules on the erythematous skin, local swelling of the lymph nodes, 3 cm in diameter, hard in consistence, painful to touch. Signs of right-sided pneumonia and pleural effusion.

Laboratory investigations: ESR 84/125 mm/h, fibrinogen 6,7 g/L (ref. value 2 - 4 g/L), CRP 197 mg/L (ref. vr. 6 mg/L), leukocytosis $24,7 \times 10^9/L$ with 70% neutrophils, 17% lymphocytes, 13% eosinophils (absolute count $3211/mm^3$), erythrocyte count $4,4 \times 10^{12}/L$, hemoglobin 10^9 g/L, hematocrit 34,1%, trombocyte count $407 \times 10^9/L$. Serum IgE concentration above 2000 IU/mL. Chest X-ray revealed right-sided destructive pneumonia with pleural effusion and pneumatocele (Fig. 3). A chest tube was inserted and 340 mL of purulent fluid was evacuated. It grew *Staphylococcus aureus* on culture. After thoracic drainage, right-sided pneumothorax developed and thoracic drainage was performed for another 16 days. The patient's destructive pneumonia resolved on treatment with antibiotics (vancomycin, later on cloxacillin) and antifungal (nystatin). He was dismissed from hospital in good condition. On the last check up, one month after hospitalization, he was infection-free, receiving daily prophylaxis with cloxacillin.

Diskusija

HIES je retka primarna imunodeficijencija u kojoj se od ranog, ponekad i neonatalnog uzrasta, mogu pojaviti teške bakterijske infekcije, kao i kožne promene u vidu pustuloznog dermatitisa [7]. U ovom sindromu opisane su i mnogobrojne skeletne anomalije kao što su dismorfija lica [8], povećan razmak između nosnih krila, poremećaj u nicanju stalnih zuba [9], hiperelastičnost zglobova [1], a deformiteti kičmenog stuba se obično registruju u kasnijem životnom dobu [10]. Česte su i spontane frakture kostiju usled patološke resorpcije koštanog tkiva uslovljene prekomernom aktivnošću IL-4 [11,12].

Poremećaji imunološkog sistema su nedovoljno objašnjeni kod bolesnika sa HIES. Nije precizno utvrđeno zbog čega kod HIES-a postoji povećana osetljivost ka infekcijama, iako su kod ovih bolesnika utvrđeni poremećaji hemotakse granulocita, kao i smanjena produkcija interferona- γ na stimulaciju sa IL-12 [13]. Kod bolesnika sa HIES je utvrđena značajno smanjena produkcija specifičnih antitela na polisaharidne antigene, što može objasniti pojavu infekcija invazivnim (inkapsuliranim) sojevima pneumokoka ili hemofilusa influence čija kapsula sadrži polisaharidne antigene [14]. Proliferacijski odgovor limfocita na specifične antigene kao što je tuberkulin i kandidin *in vitro* je najčešće snižen [15,16]. Pretpostavka je da povećana ekspresija receptora IL-13 na CD4+ limfocitima dovodi kod ovih pacijenata do ekstremnog povećanja IgE antitela [17,18]. Povišen nivo serumskog IgE čija je vrednost viša od 2000 IU/mL predstavlja dijagnostički kriterijum za HIES, iako i niže vrednosti IgE ne isključuju u potpunosti dijagnozu HIES. Kod bolesnika sa atopijskim dermatitisom se ponekad mogu utvrditi visoke koncentracije serumskog IgE, ali ovi bolesnici obično nemaju duboke, invazivne infekcije. U diferencijalnoj leukocitnoj formuli kod HIES je prisutna eozinofilija, koja je najmanje za 2 SD viša od referentnih vrednosti. U sputumu i u tkivnim apscesima takođe se mogu naći eozinofilni granulociti [1].

Genetska osnova HIES se još uvek istražuje. Analiza brojnih porodica ukazuje da se najverovatnije radi o autozomno-dominantnom tipu nasleđivanja sa varijabilnom ekspresijom. Opisane su i porodice sa verovatnim autozomno-recesivnim tipom nasleđivanja. Samo kod retkih bolesnika novija istraživanja su potvrdila da proksimalni deo q regiona na hromozomu 4 sadrži lokus za ovu bolest [19]. Sindrom se javlja kod osoba iz različitih etničkih grupa, polovi su podjednako zastupljeni, a nije češći ni u jednoj specifičnoj populaciji [1,20].

HIES je u suštini multisistemski poremećaj pri čemu je zapažen deficit imunološkog sistema i vezivno-koštanog sistema. Jedna od najčešćih infekcija kod bolesnika sa HIES je stafilokokna pneumo-

Discussion

HIES is a rare primary immunodeficiency in which severe bacterial infections, as well as skin changes (pustulous dermatitis) may develop very early, sometimes even in the neonatal period [7]. In this syndrome numerous skeletal abnormalities have been reported, such as facial dysmorphism [8], increased interaural distance, delayed eruption of permanent teeth [9], hyperextensible joints [1]. Spine deformities usually develop later in life [10]. Spontaneous bone fractures are also frequent. They occur due to pathologic resorption of bony tissue caused by excessive activity of IL-4 [11,12].

Immune system disorders in patients with HIES are still not fully understood. It is still not established why there is an increased susceptibility to infections in HIES, although it is known that in these patients impairment of granulocyte chemotaxis is evident as well as decreased production of interferon- γ on stimulation with IL-12 [13]. In patients with HIES, investigations have revealed important decrease in production of specific antibodies to polysaccharide antigens that can explain appearance of infections with invasive (encapsulated) *Pneumococcus* or *Haemophilus influenzae*, whose capsule contains polysaccharide antigens [14]. Proliferative response of lymphocytes to specific antigens such as PPD and candidin *in vitro* is usually decreased [15,16]. One can suppose that increased expression of IL-13 receptors on CD4+ lymphocytes in these patients causes extreme elevation of IgE antibodies [17,18]. Increased serum concentrations of IgE above 2000 IU/mL represents a diagnostic criteria for HIES, although even lower IgE values do not exclude completely the diagnosis of HIES. Sometimes, in patients with atopic dermatitis serum concentrations of IgE can be elevated, but these patients usually do not suffer from deep, invasive infections. Differential leukocyte formula in HIES reveals eosinophilia (at least for 2 SD higher than ref. values). Eosinophils can also be found in sputum and tissue abscesses [1].

Genetic basis of HIES is still under investigation. Analyses of numerous families show that there is most likely an autosomal dominant pattern of inheritance with variable expression. Families with probable autosomal recessive pattern of inheritance have also been reported. Only in few patients newer investigations showed that proximal region of the 4th chromosome contains a locus for this disorder [19]. HIES is present in different ethnic groups, with equal sex distribution, and it's not more common in any specific population [1,20].

nija, koja se ponekad odlikuje destrukcijom parenhima i nastankom pneumatocela kao što je bio slučaj i kod našeg pacijenta. Prodor infekcije s kože u predelu vrata, doveo je do rasapa infekcije uz prethodnu supuraciju regionalnog limfnog čvora. Primena neodgovarajuće antimikrobne terapije, uslovila je nastanak pneumonije sa pleuralnim izlivom, pneumatocelama i nastankom spontanog pneumotoraksa.

Kod pacijenta su bili prisutni neophodni dijagnostički kriterijumi za postavljanje dijagnoze HIES-a, a to su pre svega anamnestički podaci o teškim supurativnim otitisima koji su se javljali od drugog meseca života, zatim izrazito povišene vrednosti IgE i eozinofilija u diferencijalnoj beloj lozi. Bakteriološki nalaz pleuralnog punktata ukazuje da je etiološki uzročnik infekcije *Staphylococcus aureus*. Uz prisutne laboratorijske parametre naš pacijent ima i skeletne anomalije koje se prevashodno odnose na veoma neobičan izgled lobanje, posebno frontalnog dela uz ostale znake dismorfije lica, koji takode idu u prilog dijagnozi. U revijalnom prikazu 34 bolesnika sa HIES opisani su poremećaji denticije koji se odnose na zakasnelu resorpciju korena mlečnih zuba, nemogućnost izbijanja stalnih zuba i/ili pojavu dvostrukog niza zuba jer stalni zubi niču pored mlečnih [9]. Ukoliko se javi ovakav poremećaj denticije kod našeg pacijenta, problem se može rešiti blagovremenom stomatološkom intervencijom. S obzirom na trenutni uzrast našeg bolesnika za sada se ostale skeletne malformacije ne mogu procenjivati, a postoji mogućnost da će se ispoljiti kasnije u životu.

Izrada rodoslovnog stabla otkrila je pojavu hladnih apscesa kod strica deteta, koji uz to ima i neobičan izgled lica. Otac i stric imaju povišene nivoe serumskog IgE, a otac i povećan alarni dijametar. Navedeni podaci ukazuju da se kod našeg pacijenta najverovatnije radi o autozomno-dominantnom tipu nasleđivanja sa varijabilnom ekspresijom, a bolest je potpuno izražena samo kod našeg bolesnika.

Preživljavanje pacijenata sa HIES je isključivo povezano s primenom redovne, svakodnevne antibiotske profilakse antistafilokoknim lekovima. Najčešće se primenjuju semisintetski penicilini (kloksacilin, dikloksacilin) ili ponekad cefalosporini I generacije (cefadroksil) [1]. Pitanje primene redovne antigljivične profilakse ostaje otvoreno pošto ovi bolesnici mogu imati invazivne, duboke gljivične infekcije [4]. Od prevashodnog značaja je pravovremena i energična terapija svake infekcije. Preduzete preventivne mere kod našeg pacijenta do sada su imale veoma povoljan efekat. Mora se ipak naglasiti da i pored dobre antimikrobne terapije koja je danas dostupna, dugotrajno preživljavanje i trajna prognoza kod bolesnika sa ovom retkom imunodeficijencijom nije poznata.

HIES is a multisystemic disorder with deficiency of immune system and connective and bony tissues. One of the most frequent infections in patients with HIES is staphylococcal pneumonia, which is sometimes complicated with destruction of parenchyma and formation of pneumatocele, just like in our patient. Invasion of the infection from the neck region was followed by suppuration of the regional lymph node and led to dissemination of bacteria. Treatment with inappropriate antibiotic therapy led to development of pneumonia with pleural effusion, pneumatocele and spontaneous pneumothorax.

Necessary diagnostic criteria for HIES were present in our patient: history of severe purulent otitis media from the second month of life, extremely elevated serum IgE concentrations, increased eosinophyle count. Bacteriologic examination of the pleural fluid specimen revealed growth of *Staphylococcus aureus*. Apart from laboratory findings, our patient also has skeletal anomalies, such as very unusual facial features, with prominent forehead and other signs. In a review of 34 patients with HIES, different dental abnormalities were reported, such as delayed resorption of the primary teeth, impaired eruption of permanent teeth and/or appearance of teeth in two rows because primary teeth are still present while permanent teeth are erupting (9). If delayed resorption of primary teeth occurs in our patient, the problem will be solved on time by extraction. Due to the fact that our patient is only two years old, other skeletal anomalies can not be evaluated, although there is a great chance that they will eventually develop later in life.

Family pedigree of our patient demonstrated parent-to-child transmission. His father and uncle have elevated serum IgE concentration. The father has an increased interalar distance, and the uncle has unusual facial appearance and a history of frequent "cold" skin abscesses. The probable transmission pattern is autosomal dominant with variable expression. The disorder is fully expressed only in our patient.

Long term prognosis and survival of patients with HIES depends on constant daily antibiotic prophylaxis for staphylococcal infections. Semisynthetic penicillins are most frequently used (cloxacillin, dicloxacillin) and only sometimes 1st generation cephalosporins (cephadroxyl) (1). The question of daily antifungal prophylaxis remains to be answered, since these patients are prone to invasive, deep fungal infections (4). It is most important to treat every infection on time, with appropriate antibiotics. So far, daily prophylaxis in our patient is efficient. Still, we must emphasize that even though powerful antibiotics can be used today, long term survival and prognosis in patients with this rare immunodeficiency are unknown.

Zaključak

HIES je multisistemski poremećaj koji predstavlja tešku imunodeficienciju zbog bakterijskih infekcija koje mogu ugroziti život ovih bolesnika, naročito u mladem uzrastu. Zbog toga je veoma važno da se dijagnoza postavi odmah po pojavi prvih navedenih karakterističnih simptoma, znakova i laboratorijskih nalaza da bi se adekvatna terapija, prevencija i režim života pravilno sprovodili. I pored sprovedene terapije, dugoročna prognoza kod ovih bolesnika je neizvesna.

Conclusion

HIES is a multisystemic disorder and represents a severe immunodeficiency due to development of life threatening bacterial infections, especially in early ages. Therefore, it is important to diagnose the disorder as soon as possible, when the first characteristic symptoms, signs, and laboratory findings are available. In that case these patients can receive suitable treatment and prophylaxis. Even then, long term prognosis in this disorder is doubtful.

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