PRIKAZ IZ KLINIČKE PRAKSE
CASE REPORT

# EKSTRANODULARNI NON HODGKIN (MALT) LIMFOM PAROTIDNE PLJUVAČNE ŽLEZDE

# EXTRANODAL NON HODGKIN (MALT) LYMPHOMA OF PAROTID GLAND

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***Kratak sadržaj***

*Malt limfomi (Mucosa associated lymphoid tissue - MALT), su prvi put opisani 1983. godine od strane Isaacsona i Wrighta. Malt limfomi pripadaju ekstranodalnim non Hodgkin limfomima (NHL) B ćelijskog tipa. Karakterišu se prisustvom neoplastičnih marginalnih ćelija koje pokazuju različit stepen varijabilnosti u kolonizaciji germinativnih centara, plazmocitičnu diferencijaciju i destruktivnu epitelijalnu infiltraciju, formirajući limfoepitelijalne lezije tkiva. U martu mesecu 2004., u Klinici je hospitalizovana bolesnica životne starosti od 59 godina zbog operacije obostrano ekstremno uvećanih parotidnih pljuvačnih žlezda, sa veoma izraženom suvoćom usne duplje. Urađena je subtotalna parotidektomija sa leve strane, gde se tumefakt sastojao od tri lobusa. Patohistološka dijagnoza je bila MALT (MUCOSA ASSOCIATED LYMPHOID TISSUE) LYMPHOMA DIFFUSUM (dobrodiferentovan tip – B ćelijskog porekla). Predstavljen je detaljno ovaj patološki entitet, kao i njegova onkološka gradacija i način tretmana.*

***Ključne reči**: ekstra nodularni, non Hodkin, limfomi, MALT limfomi, parotidna žlezda*

***Abstract***

*Malt lymphomas (mucosa associated lymphoid tissue-MALT) are described for the first time in 1983 by Isaacson and Wright. Malt lymphomas are extranodal non Hodgkin lymphomas (NHL) of B cell type. Their characteristic is presence of neoplastic marginal cells that show diferent variability grade in colonisation of germinative centers, plasmocytic differentiation and destructive epithelial infiltration, that form lymphoepithelial tissue lesions. In march 2004, in our clinic a 59 years old woman was hospitalised for a surgical treatment of bilateral extreme swelling of both parotid glands,with significantly dry oral cavity. On the left side a subtotal parotidectomy has been done; the tumor consisted of 3 lobi. Pathohistologic diagnosis was MALT (mucosa associated lymphoid tissue) lymphoma diffusum (well diferentiated type of B cell origine). This patologic entity, its oncological gradation and treatment is fully described in the article.*

***Key words**: extranodular, non Hodking, lymphomas, MALT lymphoma, parotid gland*

## *Uvod*

MALT limfomi (Mucosa associated lymphoid tissue), su prvi put opisani 1983 godine od strane Isaacsona i Wrighta.[1,2] MALT limfomi pripadaju ekstranodalnim non Hodgkin limfomima (NHL) B ćelijskog tipa. Karakterišu se prisustvom neoplastičnih marginalnih ćelija koje pokazuju različit stepen varijabilnosti u

## *Introduction*

MALT lymphomas (mucosa associated lymphoid tissue) are described for the first time in 1983 by Isaacson and Wright.[1,2] MALT lymphomas are extranodal non Hodgkin lymphomas (NHL) of B cell type. Their characteristic is presence of neoplastic marginal cells that show

kolonizaciji germinativnih centara, plazmocitičnu diferencijaciju i destruktivnu epitelijalnu infiltraciju, formirajući limfoepitelijalne lezije tkiva[2].Trizomija 3 je verifikovana u oko 60% low-grade MALT limfoma.[4] Najčešća lokalizacija MALT limfoma je gastrointestinalni trakt. Berger i sar.[5] su opisali ukupno 43 slučajeva MALT limfoma od čega je 27 bilo gastrointestinalne lokalizacije, a ostalih 16 su lokalizovani u orbiti, parotidnoj pljuvačnoj žlezdi, plućima, tonzilama i tireoidei. Takahashi i sar.[6] su opisali 10 slučajeva MALT limfoma lokalizovanih u pljuvačnim žlezdama. 7 pacijenata je bilo sa MALT limfomom u parotidi, 2 u submandibularnoj žlezdi i 1 u sublingvalnoj žlezdi. MALT limfomi se najčešće javljaju u periodu između 3. i 5. decenije života i to češće kod žena nego kod muškaraca i to u odnosu 6:1,7.[7] Najčešći simptom kod MALT limfoma je prisustvo bolnog otoka zahvaćene pljuvačne žlezde. U oko 30% pacijenata prisutan je i sicca sindrom. MALT limfomi najčešće bivaju lokalizovani na primarnom mestu pojavljivanja i u limfnim nodusima. Diseminacija bolesti predstavlja komplikaciju u smislu pozne manifestacije.[8] Definitivna dijagnoza u slučajevima MALT limfoma je moguća samo histološkim ispitivanjem biopsijskog materijala.

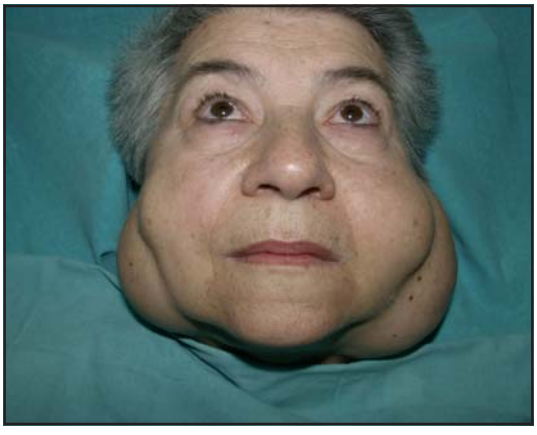
## *Prikaz bolesnika*

U martu mesecu 2004, u našoj klinici je hospitalizovana bolesnica, 59 godina stara, zbog operacije obostrano ekstremno uvećanih parotidnih pljuvačnih žlezda, sa prisutnom i veoma izraženom suvoćom usne duplje (slika 1). Bolesnica, hipertenzivnu bolest regulisala je terapijom ordiniranom od strane kardiologa, više godina unazad, a pre godinu dana operisala je oba kuka zbog coxartrose, tako da hoda pomoću štaka, veoma teško i najčešće pomoću pratioca.

diferent variability grade in colonisation of germinative centers, plasmocytic differentiation and destructive epithelial infiltration, that form lymphoepithelial tissue lesions.[3] Trisomia 3 is verified in aproximately 60% of low grade MALT lymphomas[4]. The most common localisation of MALT lymphoma is gastrointestinal tract. Berger et al.[5] described 43 cases of malt lymphoma, of wich 27 were of gastrointestinal localisation and 16 were found in orbita, parotid glands, lungs, tonssilas and thyroid gland. Takahashi et al.[6] described 10 cases of MALT lymphomas in salivary glands. 7 patients had MALT lymphomas in parotid gland, 2 in submandibular gland and 1 in sublingual gland. MALT lymphomas usually occur in the mid age, between 30 and 50 years of life. Women are affected more frequently-6: 1,7[7]. The most common symptom is presence of painful sweeling of affected parotid gland. In 30% of patients the sicca syndroma is present. MALT lymphoma is usually localised in the place of primary occurence and in lymph nodi. Dissemination of the disease is late complication.[8] In case of MALT lymphoma definitive diagnosis is possible only by histologic observance of biopsed material.

## *Case report*

In march 2004, in our clinic a 59 years old woman was hospitalised for a surgical treatment of bilateral extreme swelling of both parotid glands,with significantly dry oral cavity (Figure 1). The patient recevies antihypertensive treatment for years. One year ago both her hips were operated for coxartrosis, so she walks using crutches or with escort.

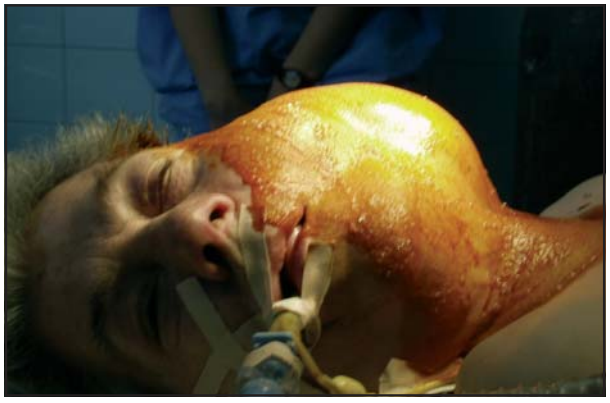


*Slika 1. Bolesnica sa Sy. Mikulić*

*Figure 1. The patient with syndroma Mikulicz*

Tumor u levoj parotidnoj pljuvačnoj žlezdi, u vidu izrasline u predelu ugla donje vilice, promera 1 cm, primetila je 1991. g. i tada nije prihvatila predloženu hiruršku intervenciju. Tumor je ubrzo počeo da se javlja i sa desne strane; oba su bila bezbolna sa tendencijom stalnog rasta. Javila se maksilofacijalnom hirurgu juna 2000.g., zbog prisutnog dodatnog tumora u levoj parotidno-maseteričnoj regiji promera 10 x 8 cm, i u obraznoj regiji sa iste strane, jasno ograničenog tumora promera 3 x 2cm, palpatorno blago bolnog. U to vreme bolesnica je navodila osećaj suvoće usne duplje. Intraoralnim pregledom ustanovljeno objektivno postojanje blagog mukozita, sa smanjenom sekrecijom pljuvačke. Tumor (promera 10 x 8 cm) u desnoj parotidnoj žlezdi je zahvatio celu parotidnu ložu i deo obraznog prostora i bio je režnjevite građe i bezbolan. Predloženu operaciju je bolesnica odbila zbog druge operacije na kukovima.

Posle ambulantne pripreme bolesnica je hospitalizovana u martu 2004. g. Uvidom u istoriju bolesti utvrđen je sledeći nalaz: prisustvo izrazito velikih tumora u oba parotido-maseterična i obrazna prostora. Levostrani tumor se sastjao iz tri tumora koja su se spajali u jedan (slika 2).



*Slika 2. Izgled leve parotidne i obrazne regija*

*Figure 2. The appearance of the left parotid and buccal region*

Desnostrani tumor je bio građen iz dva dela. Manji je bio (promera 5 x 5 cm) medijalno lociran u bukalnom prostoru, tvrde konzistencije i bezbolan. Veći tumor (promera 12 x 12 cm) zahvatao je čitavu parotido-maseteričnu ložu, deo retroangularnog i submandibularnog prostora i bio je režnjevite građe i bezbolan. Koža iznad promene pokretna, uobičajene teksture i karakteristika.

Otvaranje usta u bolesnice je bilo u granicama normale, sa atrofičnom izmenjenom sluzokožom jezika i sa prisutnim ragadama. Bila je prisutna totalna bezubost u vilicama i sindrom suvih usta.

The tumor in left parotid gland with 1 cm in diameter the patient noticed in1991, but she refused suggested surgical treatment. Another tumor appeared also on the right side. Both were painless,with intention of constant growth. She visit a maxillofacial surgeon in June 2000, for another tumor 10x8cm in diameter, in the left parotid-masseteric region, and another one, 3x2cm in diameter in the left buccal region, slightly painful on palpation. The patient reported the sensation of the dry mouth.After intraoral examination, the presence of light mucositis with diminished secretion of the saliva was found. The tumor (10x8cm in diameter) occupied the whole right parotid region and a part of the buccal region, had lobular structure and was painless. The proposed surgical treatment the patient refused for the hip operation.

After ambulatory preparation, the patient was hospitalised in March 2004. From the case history, the presence of significantly large tumors in both parotid and masseteric region and both buccal region was confirmed. The left sided tumor consisted of 3 smaller tumors that fused into one (Figure 2).

The tumor on the right side consisted of 2 parts. The smaller tumor (5x5 cm in diameter) was painless and located medialy in buccal region. The bigger tumor (12x12 cm in diameter) occupied the whole parotido-masseteric region, part of the retroangular and submandibular region and it was with lobular structure and painless. The skin above the tumor was movable with regular texture and characteristics.

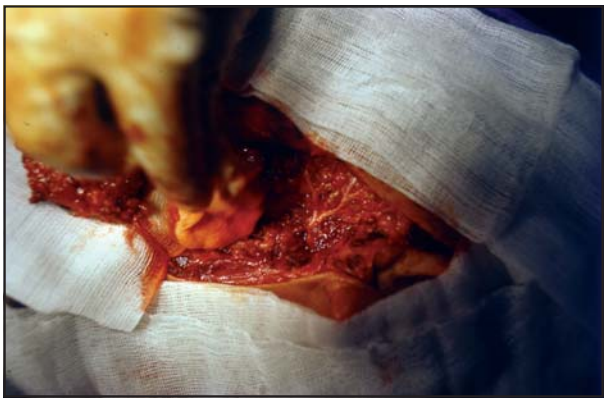
The patient was able to open the mouth normally. The lingual mucosa was atrophic with ragades. Both maxilla and mandibula was edentulous and dry mouth syndroma was present. Other symptoms, like diminished tear secretion, were absent.

Bolesnica bez promena na očima, u smislu smanjene sekrecije suza.

Posle preoperativne pripreme urađena je subtotalna parotidektomija sa leve strane, gde se tumor sastojao od tri lobusa (slike 3 i 4). Urađeno je uklanjanje površnog režnja parotidne žlezde i okolnih akcesornih žlezda uz evakuaciju celokupnog tumora u obraznoj regiji. Postoperativni tok je protekao uredno, bez lezija facijalisa (slika 5).

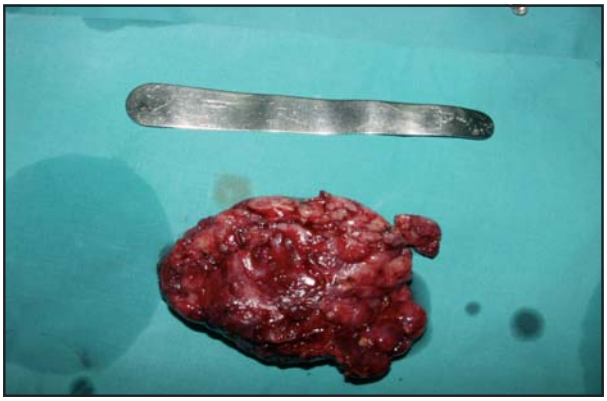
After that left subtotal parotidectomy was performed (figure 3 and 4). The tumefact consisted of 3 lobi. The superficial lobus of parotid and glands were removed with evacuation of the occessory whole tumor in buccal region. The postoperative course was regular, without lesions of the facial nerve (figure 5).

After the material was received it was prepared and stained (HE, AB-PAS, LSAB2, ABC,



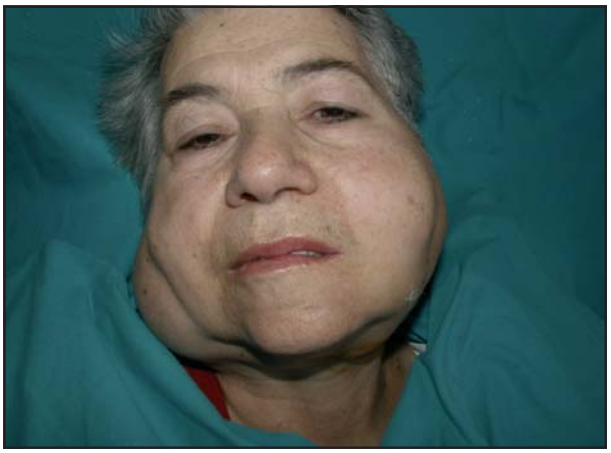
*Slika 3. Identifikovano stablo facijalisa*

*Figure 3. Identified trunk of the facial nerve*



*Slika 4. Preparat nakon parotidektomije*

*Figure 4. Post-parotidectomy specimen*



*Slika 5. Izgled bolesnice dve nedelje nakon operacije*

*Figure 5. The patient two weeks after surgery*

Nakon prijema materijala, isti je sečen, kalupljen i bojen HE, AB-PAS, LSAB2, ABC, Retikulin i Van- Gieson, kao i bojenje na citokeratin koji je patognomoničan za MALT limfom.

Histopatološke karakteristike su pokazale periduktalni i perivaskularni limfocitni infiltrat, koji gradi prave limfne folikule sa hiperplastičnim germinativnim centrima. Pokrovni epitel duktusa je hiperplastičan, što izaziva obstrukciju. Parenhim je atrofičan uz fibrozu i lipo-

reticulin and Van Gienson) and also stained on cytocheratin, patognomonic for malt lymphoma.

Patohystological charasteristic are periductal and perivascular lymphocytic infiltration that forms real lymphatic follicules with hyperplastic germinative centers. Hyperplastic changes of the epithelium of the duct are present, wich causes obstruction. Parenchyma is athrophic and associated with fibrosis, lipomatosis, and presence of smaller and larger areas of oncocytic degenera-

matozu. U sklopu atrofije parenhima zapažaju se mala i veća polja onkocitne degeneracije. Prisutna je markantna hiperplazija centrocita, uz infiltraciju strome između limfnih folikula i germinativnih centara, sa perifernom "mantle" zonom B ćelijskog tipa.

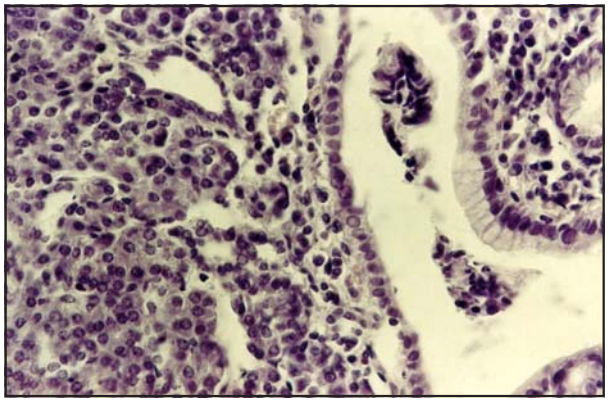
Patohistološka dijagnoza je bila: MALT (mucosa associated lymphoid tissue) lymphoma diffusum (dobrodiferentovan tip – B ćelijskog porekla). Syaloadenitis calculosa chronica (pseudocystica) (slike 6, 7, 8, 9).

Bolesnica je opservirana ultrazvučno i konstatovan je nalaz bez osobenosti. Zbog povremenih gastričnih tegoba konsultovan gastroenterolog zbog Dg: Gastritis chronica. Bolesnica je primala terapiju doksiciklin 100mg, metronidazol 500mg, omeperazol 20mg, bizmut 100gm 3 puta na dan, u trajanju od dve nedelje.

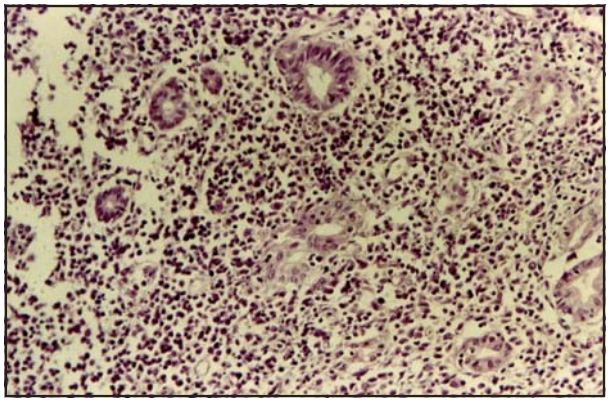
tion. A significant hyperplasia of centrocytes with infiltration of stroma between lymphatic follicules and germinative centers, with peripheric "mantle" zone of B cell type, is also present.

Patohystologic diagnosis: MALT (mucosa associated lymphoid tissue) lymphoma diffusum (well diferentiated type of B cell origine). Syaloadenitis calculosa chronica (pseudocystica) (Figure 6, 7, 8, 9).

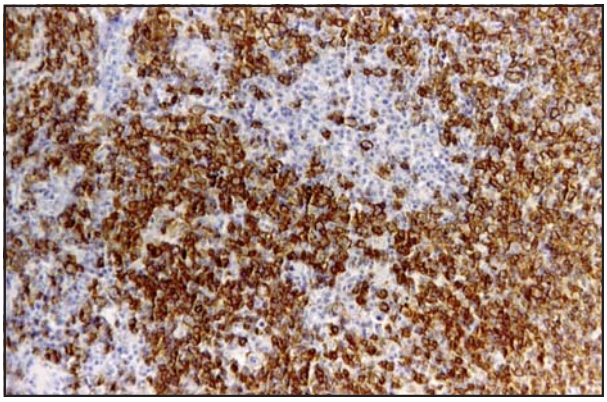
Next performed was the ultrasound examination, with regular findings. Because of occasional gastric symptoms of the patient, a gastroenterologist was consulted (Dg: Gastritis chronica). The patient received doxycycline 100mg, metronidasol 500mg, omeperasol 20mg, bismuth 100mg 3 times daily, for 2 weeks).



*Slika 6. Cistična dilatacija duktusa i gust infiltrat od hiperplastičnih plazmocita. HE x 300*
*Figure 6. Cystic ductal dilatation with hyperplastic plasmocytic infiltration. HE x 300*



*Slika 7. Gust limfocitni infiltrat uz invaziju i destrukciju. HE x 200*
*Figure 7. Lymphocytic infiltration with invasion and destruction. HE x 200*



*Slika 8. Intenzivna membranska ekspresija CD 20 antigena. LSAB2 x 250*
*Figure 8. Intensive membrane expresion of CD 20 antigene. LSAB 2 x 250*

*Slika 9. Malt limfom parotide (makroskopski preparat nakon obrade)*
*Figure 9. Malt lymphoma of parotid gland (macroscopic specimen)*

Bolesnica je prikazana Konzilijumu za limfome i odlučeno je da se sprovode redovne kontrole kod operatora. Bolesnica je redovno kontrolisana i nakon ordinirane terapije nastupila je regresija promene u desnoj parotidnoj loži za 50%.

## *Diskusija*

MALT limfom se može dijagnostikovati patohistološkom analizom posle biopsije same promene. Inciziona biopsija tumorske lezije parotidne žlezde je kontraindikovana zbog rizika od rasejavanja tumorskih ćelija, kao i zbog eventualne lezije facijalisa i stvaranja salivarne fistule. Fine-needle aspiraciona biopsija za citološku dijagnozu može biti vrlo diskutabilna u dijagnostici tumora pljuvačnih žlezda. Po navodima Stewarta i sar.[9] može doći do insuflacije neadekvatnog materijala, što može dovesti do ne mogućnosti postavljanja tačne patohistološke dijagnoze, a u boljem slučaju do nemogućnosti klasifikacije stepena malignosti promene, a samim tim i terapijske procedure. Mišljenja smo da je eksciziona biopsija, u smislu parotidektomije daleko bolja za postavljane prave dijagnoze procesa, što se slaže sa stanovištem Stewarta i sar.[9]

Još uvek ne postoji specifični marker za MALT limfom. Dokazivanje restrikcije imunoglobulinskih lakih lanaca je značajno u ddg. od benignih limfoidnih infiltrata, negativna ekspresija CD 5 služi za razlikovanje od "mantle" ćelijskog i limfoma tipa malih limfocita. CD 10 se koristi u ddg od folikularnog limfoma. Ova bojenja omogućavaju diferencijaciju MALT limfoma na low i high grade.[9,10]

MALT limfomi parotidne pljuvačne žlezde su podeljeni prema Ann Arbor klasifikaciji u IV stadijuma. Kod stadijuma I i II (low grade MALT) indikovana je hirurška terapija u kombinaciji sa subsekventnom radioterapijom, kod prisutnih znakova stadijuma III i IV neophodna je hemoterapija.[11,12]

Poznata je činjenica da MALT limfomi imaju visok nivo senzibilnosti na hemoterapiju, zato su pacijenti sa znacima diseminovane bolesti tretirani hemoterapijom. Pacijenti sa limfomima nodalne lokalizacije su najčešće podvrgavani lokalnoj radioterapiji, dok se u slučajevima prisutnih ekstranodalnih limfoma primenjena hirurška terapija. Alkan i sar.[12] su prvi objavili slučaj pa-

The patient was presented to the Comission for treatment of lymphomas in Clinic for oncology in Clinical centre Nish, that suggested regular control examination of the surgeon.The controls showed a 50% regression of the tumor in the right parotid gland after medicamentous treatment.

## *Discussion*

Malt lymphoma may be diagnosed by pathohistologic analysis after the biopsy of the alteration. Incisional biopsy of the parotid gland tumor is contraindicated because of the risk of dissemination of tumor cells and eventual lesion of the facial nerve, and creation of the salivar fistule. A fine needle aspirational biopsy for citological diagnosis is also under question for diagnosis of the salivar gland tumor. According to Stewart and al.[9] the non suitable material may be insuflated, that may impede correct patohistologic diagnosis or correct classification of the malignancy grade of the tumor, and therefore lead to an incorrect treatment. We think that the excisional biopsy-parotidectomy – is much better solution for a posing a correct diagnosis of the patologic process, which is in accordance with findings of Stewart et al.[9]

A specific marker for MALT lymphoma still does not exist. To prove restriction of imunoglobuline light chains is important for differential diagnosis of benign lymphoid infiltrations. A negative CD 5 expression is used for differentiating from "mantle" cell lymphoma, and small lymphocyte lymphoma. CD 10 is used for differential diagnosis of follicular lymphoma. These stains enable differentiation of MALT lymphoma on low and high grade.[9,10]

According to the Ann Arbor classification, MALT lymphomas are classified in 4 grades. In stadium I and II (low grade maltoma), a surgical therapy with subsequent radiotherapy is reccomended. If signs of grade III and IV are present, chemotherapy is necessary.[11,12]

Well known is the fact that MALT lymphomy have a high level of sensitivity on chemotherapy; thus patients with dissemination of the disease receive this kind of treatment .

Patients with lymphomas of nodal localisation usually receive local radiotherapy. In cases of presence of extranodal lymphomas surgical

cijenta koji je sa MALT limfomom parotidne žlezde odbio konvencionalnu terapiju. Imajući u vidu da je kod istog verifikovana gastrointestinalna infekcija Helicobacterom pylori ordinirana je antibiotska terapija u trajanju od 2 sedmice (doksiciklin 100mg, metronidazol 500mg, omeperazol 20mg, bizmut 100mg 3 puta na dan) tumorska masa u parotidnoj žlezdi je nestala, a NMR opservacijom je posle 22 meseca dokazano odsustvo bolesti. Sa druge strane hirurška terapija u smislu superficijalne ili totalne parotidektomije sa konzervacijom facijalnog nerva bez dodatnih terapijskih procedura takođe može dovesti do odsustva rekurentnosti za dug vremenski period i do 11 godina.

Naša bolesnica je tretirana na isti način, pomenuta procedura dala je poboljšanje, imajući u vidu da je došlo do redukcije promene desne parotide za 50%, što je i prihvatljiva činjenica imajući u vidu da se radi u osnovi o Mikulićevom oboljenju.

Radioterapija kao samostalni modalitet tretmana MALT limfoma veoma je teško prihvaćena s obzirom da dovodi do egzacerbacije prethodno prisutne kserostomije i pojave bolnog oralnog mukozitisa. Njene prednosti u odnosu na hiruršku terapiju su regresija tumorske mase i odsustvo ožiljka i moguća je u bolesnika sa low - grade promenom (st. I i II), nodalnog oblika.

## *Zaključak*

Dosadašnji postoperativni tok naše bolesnice je sasvim zadovoljavajući, s obzirom na njeno opšte stanje, operaciju kukova, redukciju procesa desne parotide, kao i dugogodišnju evoluciju bolesti. Ako se na adekvatan način i u adekvatno vreme dođe do prave dijagnoze, terapija ove vrste limfoma može biti ohrabrujući ishod.

treatment is reccomended. The first case of MALT lymphoma of the parotid gland that refused conventional therapy was described by Alkan et al.[12] Bearing in mind verified gastrointestinal infection with Helicobacter pylori, the patient received antibiotic therapy for two weeks (doxycycline 100mg, metronidasol 500mg, omeperasol 20mg, bismuth 100mg 3 times daily). The tumor of the parotid gland dissapeared and NMR showed complete abscence of the disease after 22 months. On the other side, superficial or total parotidectomy with preservation of the facial nerve without additional treatment, may also lead to a long period withdrawal of the disease up to 11 years.

Our patient was treated in the same way , the described procedure lead to a clinical improvement (50% reduction of the tumor in the right parotide gland), which is acceptable bearing in mind Mikulicz disease in the basis of disease.

Radiotherapy as only treatment of MALT lymphoma is accepted with difficulties, as it leads to the exacerbation of previously present xserostomia and to painful oral mucositis. Regression of the tumor and lack of cicatrix, however, are the advantages regarding surgery. This kind of treatment is possible in patients with low grade nodal maltoma (grade I and II).

## *Conclusion*

The post surgical clinical courve in our patient was satisfying bearing in mind her clinical state, surgery of the hips, the right parotide gland tumor reduction and long evolution of the disease. If the diagnosis of the disease is set in adequate way and on time, the treatment of this kind of lymphoma may have good outcome.

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