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CASE REPORT

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Burkittov limfom u obliku maksilarne otekline kod HIV-negativne odrasle osobe

Burkitt's Lymphoma Presenting as a Maxillary Swelling in a HIV-Negative Adult

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Sažetak
Burkitov limfom agresivni je oblik non-Hodginova limfoma B-stanica. U ovom prikazu dajemo presjek podataka o tom limfomu iz literature i ukratko navodimo njegove kliničke, etiološke, genske i histopatološke aspekte. Opisujemo i slučaj Burkitova limfoma u obliku maksilarne otekline kod HIV-negativnog 35-godišnjeg muškarca crne rase. Klinički izgled toga limfoma može se zamijeniti s nizom poremećaja u usnoj šupljini. Moramo istaknuti da je za njegovo rano otkrivanje u usnoj šupljini i u maksilofacijalnom području nužno razumijevanje bolesti i njezine etiologije te pravodobni diferencijalnodijagnostički postupak. Samo će se tako izbjeći prekasna i neodgovarajuća terapija.

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Ključne riječi
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Uvod

Burkittov limfom (BL) prvi je opisao Sir Albert Cook kada je u Istočnoj Africi uočio istovrsne maligne promjene među afričkom djecom koje su uglavnom zahvaćale čeljust, a ponekad i određene trbušne organe (1). Dennis Burkitt objavio je 1958. svoja opažanja nakon boravka u području endemske malarije u Ugandi i istaknuo kako je na licima tamošnje djece vidio slične otekline. Kod nekih je otkrio i abdominalnu masu, pa je za te lezije rekao da je to *sarkom koji napada afričku djecu* (2).

BL je maligna monoklonarna proliferacija mladih B-limfocita koji se dijele svakih 25 sati i šest minuta i imaju frakciju rasta od gotovo 100 posto, što ga možda čini tumorom koji najbrže raste (3). Opisane su tri podvrste BL-a: endemska (afrička), sporadična (američka) i imunodeficijentna. Sporadična vrsta pojavljuje kod djece i mladih ljudi, a pogađa u manje od 10 posto slučajeva kosti lica i ostala ekstranodalna mjesta na glavi i vratu.

Ta zloćudna novotvorina usko je povezana s infekcijom HIV-om i u nekim istraživanjima autori ističu da je tisuću puta češća kod pacijenata s AIDS-om (sidom) negoli u općoj populaciji (4). HIV nije izravno uključen u limfomato-

Introduction

Burkitt's lymphoma (BL) was first described by Sir Albert Cook in East Africa, who noticed a common malignancy among young African children that predominantly affected the jaws and sometime various abdominal organs (1). In 1958, Dennis Burkitt published his finding in areas endemic for malaria in Uganda, East Africa. He noticed similar lesions on the faces of young African children, and also detected abdominal masses in some cases and described the lesions as "sarcoma involving the jaw in African children" (2).

BL is a malignant monoclonal proliferation of early B-lymphocytes that has a potential doubling time of 25.6h and a growth fraction of nearly 100%, making it perhaps the most rapidly dividing tumour known (3). Three subtypes of BL have been described: endemic (African), sporadic (American), and immunodeficient. The sporadic form occurs in children and young adults affecting the facial bones and other extranodal sites in the head and neck in fewer than 10% of the cases.

This malignant tumor is strongly associated with HIV infection and some studies suggest that BL is at least a 1000 times more common in patients with AIDS than in the gen-

genezu, ali jest neizravno preko poremećaja regulacije citokina, kronične stimulacije antigenom i smanjenog imunosnog nadzora (5, 6).

Prikaz slučaja

Muškarac crne rase u dobi od 35 godina primljen je u bolnicu Mandaqui u brazilskom gradu São Paulu radi procjene bezbolne lezije na maksili koja se razvila tijekom dva mjeseca. Ekstraoralnim pregledom ustanovljena je oteklina lijevoga nosnog krila i područja oko lijevog očnjaka. Intraoralnim pregledom otkrivena je tumorska masa u lijevom dijelu prednje maksile sve do središnje linije u promjeru velika 4 x 3 centimetra. Masa je bila ulcerirana, slobodna i nije bila vezana za donje zube. Nakon toga je radiološkom dijagnostikom – okluzalnim i periapikalnim radiogramom – otkrivena difuzna osteolitička lezija. Na kraju je na temelju kliničkih i radiografskih pretraga postavljena dijagnoza maligne mezenhimalne neoplazme (slika 1.).

Obavljena je i incizijska biopsija tumora koja je pokazala zloćudnu novotvorinu limfnog podrijetla. Stanice su bile srednje i velike s hiperkromatičnom jezgrom i izraženim jezgricama te oskudnom citoplazmom. Imale su slabo definirane stanične rubove i bile su razmještene kohezivno, u plošnoj proliferaciji u sklopu područja *lamina propria*. Neke neoplastične stanice ulazile su u epitelne stanice iznad. Mnogobrojni makrofagi bili su mjestimice između limfoblasta, što je rezultiralo izgledom *zvjezdanog neba* (slika 2.). Zatim su limfne stanice obojene imunohistokemijskom metodom korištenjem protutijela. Tumorske stanice bile su izrazito obilježene biljegom CD 20 te slabo pozitivne na CD 79a. Nekoliko stanica pokazivalo je slabu reaktivnost na CD 10. Hibridizacija *in situ* na Epstein-Barrov virus (EBV) bila je negativna (slika 3.).

Na kraju pretraga postavljena je dijagnoza BL-a i pacijent je upućen na Onkološki odjel gdje su liječnici trebali odrediti terapiju. Tijekom fizikalnog pregleda i slikanja kod toga bolesnika nije bio pronađen ni jedan drugi tumor. Serologija na HIV bila je negativna. Primio je nekoliko ciklusa intenzivne kemoterapije, pa je na kontroli poslije šest mjeseci bolest bila u remisiji.

Rasprava

BL, najprije opisan u Istočnoj Africi, agresivni je oblik non-Hodginova limfoma B- stanica. Ima specifične morfološke i imunofenotipske značajke i visok stupanj proliferacije, a na molekularnoj razini pojavljuje se kromosomska translokacija na onkogenu MYC (7,8).

Karakteristično svojstvo BL-a je translokacija između gena za c-myc i IgH (kod 80% slučajeva t(8;14)) ili između gena za c-myc i gena za kappa ili lambda lanac IgL (u preostalih 20% slučajeva [t(2;8)], odnosno t(8;22)) (5). Gen myc podreguliran je kada se stanice terminalno izdiferenciraju (ili kada limfne stanice postanu memorijski limfociti). Preregulacija c-myc-a ima kao posljedicu neprestano proliferativno stanje i mnogo učinaka na progresiju kroz stanični ciklus, staničnu diferencijaciju, apoptozu i staničnu adheziju (9).

eral population (4). HIV is not directly involved in lymphomagenesis, but is indirectly involved via cytokine desregulation, chronic antigenic stimulation, and decreased immune surveillance (5,6).

Case report

A 35-year-old black man was admitted to the Mandaqui Hospital in São Paulo, Brazil, for evaluation of a painless lesion involving the maxilla, which developed over a 2 month period. The extra-oral examination showed a swelling in the left nasal wing and left canine area. The intra-oral examination revealed a tumoral mass in the left portion of the anterior maxilla extending through the midline, measuring 4 x 3 cm in diameter. The mass was ulcerated, friable, and revealed a negative imprint of the inferior teeth. The radiographic studies included occlusal and periapical x-rays that revealed a diffuse osteolytic lesion. Based on the clinical and radiologic features, a clinical diagnosis of a malignant mesenchymal neoplasm was made (Figure 1).

An incisional biopsy of the tumour was performed and showed a malignant neoplasm of lymphoid cell origin. The cells were medium and large in size, had hyperchromatic nuclei, prominent nucleoli, scanty cytoplasm, poorly defined cellular limits, and were arranged in a cohesive, sheet-like proliferation within the lamina propria. Neoplastic cells sometimes invaded the overlying epithelia. Numerous macrophages were interspersed among the lymphoblasts, resulting in a "starry sky" appearance (Figure 2).

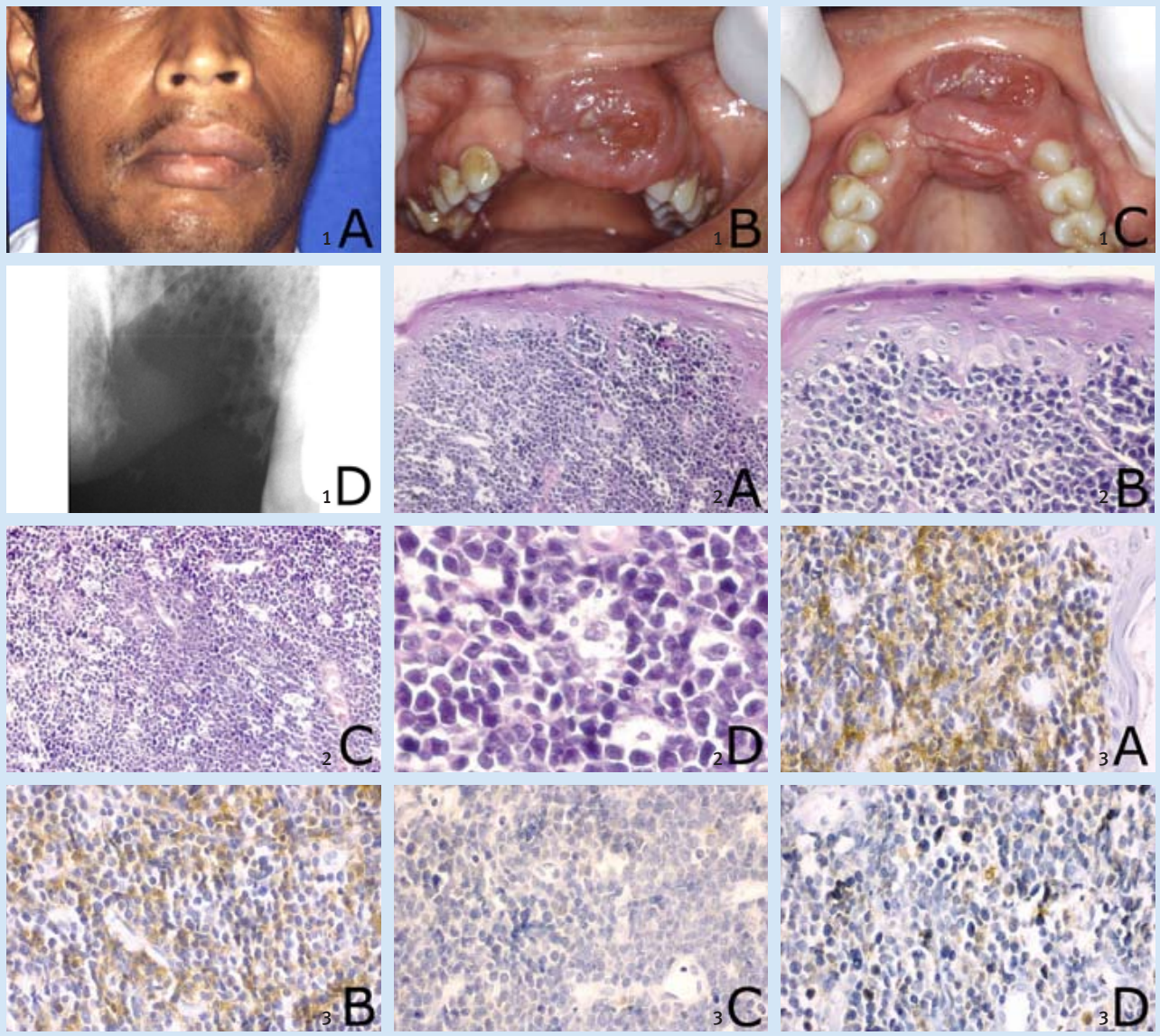
An immunohistochemical study was performed using a panel of antibodies against lymphoid cells. The neoplastic cells were strongly marked for CD20 and weakly positive for CD79a. In a few cells, a weak immunoreaction for CD10 was also noted. *In situ* hybridization for Epstein-Barr virus (EBV) was negative (Figure 3).

The diagnosis of BL was made and the patient was referred to the oncology service for evaluation and treatment. No other tumour was found in the patient by physical examination and imaging. Serology for HIV was negative. Several courses of intensive chemotherapy were administered, resulting in considerable remission up to 6 months of follow-up.

Discussion

BL, originally described in East Africa, is an aggressive form of non-Hodgkin´s B-cell lymphoma. It is characterized by specific morphologic and immunophenotypic features, a high proliferation rate, and at the molecular level, a chromosomal translocation involving the *MYC* oncogene (7,8).

A defining feature of BL is the presence of translocation between the *c-myc* and IgH genes (found in 80% of cases [t(8;14)]) or between *c-myc* and the gene for either the kappa or lambda light chain [IgL] in the remaining 20% [t(2;8) or t (8;22), respectively]) (5). The gene *myc* is downregulated when the cells are terminally differentiated (or when lymphoid cells become memory lymphocytes). *c-myc* rearrangement results in a perpetually proliferative state, and has wide-ranging effects on progression through the cell cycle, cellular differentiation, apoptosis, and cell adhesion (9).



Slika 1. Klinički i radiološki izgled lezije – maksilarna oteklina nalazi se na pacijentovoj lijevoj strani (A); oralnim pregledom otkrivena je ulcerativna masa na lijevom dijelu prednje maksile (B, C); periapikalni radiogram pokazuje difuznu osteolitičnu leziju (D)

Figure 1 Clinical and radiographic aspects of the lesion. A maxillary swelling was noted on the patient's left side (A). The oral examination revealed an ulcerative mass in the left portion of the anterior maxilla (B, C). A periapical x-ray showed a diffuse osteolityc lesion. (D)

Slika 2. Histopatološki nalaz pokazuje malignu neoplazmu limfnih stanica poredanih u guste slojevite formacije koje proliferiraju unutar područja *lamina propria* (A; H/E bojenje, originalno povećanje x 100); neoplastične stanice ponegdje su i u epitelu (B; H/E bojenje, originalno povećanje x 200); izgled *zvjezdanog neba* kao rezultat nekoliko uguranih makrofaga između neoplastičnih stanica (C; H/E bojenje, originalno povećanje x 100); limfoidne neoplastične stanice bile su srednje do velike, imale su hiperkromatične jezgre i izražene jezgrice, siromašnu citoplazmu i slabo definirane stanične rubove (D; H/E bojenje, originalno povećanje x 400)

Figure 2 Histopathologic examination shows a malignant neoplasm of lymphoid cells arranged in a dense sheet-like proliferation within the lamina propria (A; H/E stain, original magnification x100). Neoplastic cells were sometimes present in the underlying epithelia (B; H&E stain, original magnification x200). A starry sky appearance was found as a result of several macrophages interspersed among the neoplastic cells (C; H&E stain, original magnification x100). Lymphoid neoplastic cells were medium-to-large in size, had hyperchromatic nuclei, prominent nucleoli, scanty cytoplasm, and poorly defined cellular limits (D; H&E stain, original magnification x400).

Slika 3. Neoplastične stanice snažno pozitivne na CD 20 (A i B; streptavidin-biotin tehnika, originalno povećanje x 200) i slabo pozitivne na CD 79a (C; streptavidin-biotin tehnika, originalno povećanje x 200); vide se također poneke pozitivne stanice CD 10 (D; streptavidin-biotin tehnika, originalno povećanje x 200)

Figure 3 Neoplastic cells strongly positive for CD20 (A and B; streptavidin-biotin technique, original magnification x200) and weakly positive for CD79a (C; streptavidin-biotin technique, original magnification x200). Some CD10-positive cells are also observed (D; streptavidin-biotin technique, original magnification x200).

Također se zna da se EBV smatra potencijalnim etiološkim čimbenikom BL-a (10). U mnogim istraživanjima istaknuto je da EBV nakon ulaska u orofarings i susjedne strukture najprije inficira B-stanice preko receptora CD 21 i C 2d komponente komplementa.

Virus postaje stalna infekcija zbog latencije u B-stanicama. To stanje prestaje samo kada su pojačani EBNA 1 – nuklearni antigen i EBER – mali nekodirajući RNK. EBER inhibira apoptotičke putove i pokreće interleukin (IL-10) koji može pojačati signale za proliferaciju i potencijalno postaje osnova za onkogenezu (6, 10). EBV snižava antigenski protein i inicijaciju litičkog ciklusa virusa te ga prati i smanjenje MHC-a klase I i II na staničnoj površini (6, 11). Približno 90 posto afričke populacije s BL-om ima EBV DNK, a samo 20 posto sa sporadičnim oblikom povezano je s EBV-om (10). Opisani slučaj bio je EBV-negativan na hibridizaciju *in situ*. Prema klasifikaciji Svjetske zdravstvene organizacije (WHO), opisana su tri klinička oblika BL-a: endemični – obično pogađa afričku djecu u dobi od 4 do 7 godina; sporadični – pojavljuje se diljem svijeta i obično se dijagnosticira kod djece i mladih ljudi, a rijetko kod sredovječnih (12); te oblik povezan s imunodeficijencijom (13, 14). Endemski oblik treći je po učestalosti solidni tumor koji pogađa djecu u Africi, češći su samo tumor mozga i Wilmov tumor (13). Taj oblik uglavnom zahvaća mandibulu, maksilu i abdomen. Sporadični se oblik, pak, obično pojavljuje kao masa u trbušnoj šupljini i zahvaća mezenterične limfne čvorove ili ileocekalnu regiju (6, 9). Čeljust je zahvaćena samo u sedam do 18 posto slučajeva (10).

U sjeveroistočnom Brazilu opisano je 86 pacijenata s BL-om prosječne dobi 6,1 godina, a omjer muškaraca i žena iznosio je 2,4:1. Kod 60 posto bolesnika postojao je abdominalni tumor kao primarno mjesto bolesti (15). Ti rezultati pokazuju da BL ima u Brazilu sličnu pojavnost kao afrički oblik kod kojega su klinička obilježja u osnovi abdominalna, slično kao kod sporadičnog BL-a (15).

Ovdje opisani slučaj pacijenta bio je izvan vrhunca dobne incidencije BL-a u neendemičnom području i bez abdominalnih masa, za razliku od podataka iz istraživanja u kojima je istaknuto da je kod odraslih pacijenata abdomen najčešće zahvaćen (9). Među znakovima i simptomima oralnoga BL-a su mobilni zubi, oralna masa, proširenje desni, bol, rast čeljusti, otekline i poremećaj osjeta, a najuobičajeniji su bolovi (6, 10). U opisanom slučaju nije bilo bolova i maksilarne lezije. Lokacija i početak u tumora u čeljustima varira, kao što se i navodi u literaturi. U jednom istraživanju provedenom u Kanadi ističe se da je mandibula češće zahvaćena nego maksila (10). Suprotno tome, u deskriptivnom istraživanju djece i adolescenata u Libiji pronađeno je, pak, da je maksila češće pogođena nego mandibula (16). Ta diskrepancija može se objasniti razlikom u rasi i državi (6, 10). U slučaju analiziranom u ovom istraživanju, tumorska masa nastala je u prednjoj maksili. BL može biti nalik na razne agresivne orofacijalne patologije, uključujući akutni dentoalveolarni apsces, osteomijelitis, rabdomiosarkom, periapikalnu leziju, ameloblastom, eozinofilni granulom, multipli mijelom, leukemije i druge fibrokoštane lezije. Zato se, prema potrebi, treba primijeniti diferencijalna dijagnoza (5, 17). Ulcerativna intrau-

Additionally, it is known that EBV is considered to be a potential etiologic factor for BL (10). Many studies have found that EBV, after entering the oropharynx and adjacent structures, preferentially infects B-cells via the C3d complement receptor, CD21. The virus establishes persistent infection through its latency in B cells. A latency pattern of EBV gene expression exists in which only EBNA1, a nuclear antigen, and the EBERs, small non-coding RNAs, are expressed. EBERs inhibit apoptotic pathways and induce expression of interleukin (IL)-10, which may result in increased proliferative signals, potentially forming the basis of oncogenesis (6,10). In addition, EBV reduces antigenic protein expression and the initiation of the lytic cycle of the virus is accompanied by a marked reduction of MHC class I and II expression at the cell surface (6,11).

Approximately 90% of African BLs contain EBV DNA, whereas only 20% of sporadic BL are associated with EBV (10). The current case was EBV-negative by *in situ* hybridization.

According to the World Health Organization (WHO) classification, three clinical variants of BL have been described: endemic, which usually affects 4-7-year-old Africans; sporadic, occuring worldwide and usually diagnosed in children and young adults, but rarely in middle-aged adults (12); and the immunodeficiency-associated type (13,14). The endemic form is the third most commom solid tumour affecting children in Africa, exceeded only by brain tumours and Wilm's tumour (13). This form typically involves the mandible, maxilla, and abdomen. In contrast, the sporadic form commonly presents as an abdominal mass involving the mesenteric lymph nodes or ileocecal region (6, 9). The jaws are affected in only 7%-18% of sporadic cases (10).

In Northeast Brazil, a case series of 86 patients with BL reported that the avarage age was 6.1 years, the male/female ratio was 2.4:1, and > 60% presented an abdominal tumor as the primary disease site (15). These findings suggests that BL in Brazil has a similar pattern of frequency to African BL, although the clinical presentation is essentially abdominal, similar to sporadic BL (15). The patient reported herein was beyond the peak incidence age for BL in non-endemic regions and no abdominal masses were present, in contrast with a study which showed that in adult patients, the abdomen is the most frequent site of involvement (9).

Signs and symptoms of oral BL, including mobile teeth, oral masses, gingival enlargement, pain, jaw expansion, swelling and sensory disturbances, have been recorded by some workers, with pain being the most common presenting symptom (6,10). The current case was characterized by a lack of pain and a maxillary lesion.

The location of onset in the jaws varies in the case series reported in the literature. A Canadian study showed that the mandible was more affected than the maxilla (10). In contrast, a descriptive study in Libyan children and adolescents reported that the maxilla was more affected than the mandible (16). This discrepancy may be caused by differences in country and the patient race (6,10). In the current case, the tumor mass was in the anterior maxilla.

BL can mimic various types of aggressive orofacial pathologies, including acute dentolalveolar abscesses, osteomyelitis,

terina oteklina, uz opsežno razaranje kosti, upućuje na zloćudnu novotvorinu. Opisani slučaj imao je te značajke pa je rana dijagnoza bila vrlo važna jer je početak i razvoj neoplazme brz i da se nije odmah počelo s liječenjem ishod bi bio koban (6, 15). BL, bez obzira na podvrstu, tipično pokazuje monotipni IgM i pan-B-stanične antigene (uključujući CD 19, CD 20, CD 22 i CD 79a), uz koekspresiju CD 10, Bcl-6, CD 43 i p 53 (5). U našem slučaju nastala je jaka pozitivna reakcija na CD 20 i slabo pozitivna na CD 79a. U nekim područjima uočena je i imunoreaktivnost na CD 10. Odrasli pacijenti gotovo su uvijek pogođeni i AIDS-om (sidom). BL čini 40 posto non-Hodginovih limfoma povezanih s HIV-om. Relativni rizik od non-Hodgkinova limfoma je 60 do 200 puta veći kod HIV-pozitivnih osoba negoli onih iz opće populacije (4). Prevelika ekspresija onkogena c-myc i gubitak funkcije divljeg tipa gena p 53 također se smatraju mogućim etiološkim čimbenikom. Imunodeficijentni pacijenti, posebice oni s AIDS-om i ljudi s presađenim srcima ili bubrezima, podložniji su razvoju BL-a. U našem slučaju pacijent je bio HIV-negativan (8, 9).

Zaključak

Iz ovog prikaza slučaja jasno je da se klinički oblik BL-a može zamijeniti s različitim poremećajima u usnoj šupljini. Razumijevanje ove bolesti i njezine etiologije, uključujući i diferencijalnu dijagnozu, nužno je za njezino rano otkrivanje u oralnom i maksilofacijalnom području. Jedino će se tako izbjeći odgađanja liječenja ili primjena neodgovarajuće terapije.

rhabdomyosarcomas, periapical lesions, ameloblastomas, eosinophilic granulomas, multiple myelomas, leukemias, and other fibro-osseus lesions, so the establishment of differential diagnosis is necessary (5,17). An ulcerative intra-oral swelling with extensive bone destruction suggests a malignant neoplasm. The present case showed these features and the early diagnosis was important since the onset and progress of this neoplasm is said to be rapid, and if not promptly treated, runs a fatal course (6,15).

BL, regardless of subtype, typically expresses monotypic surface IgM, pan-B-cell antigens (including CD19, CD20, CD22, and CD79a), and co-expresses CD10, Bcl-6, CD43, and p53 (5). In our case, we found strong positivity for CD20 and weak positivity for CD79a. In some areas, immunoreaction with CD10 was also observed.

Adult BL patients are almost always affected by AIDS. BL accounts for 40% of HIV-associated non-Hodgkins lymphoma cases. The relative risk of non-Hodgkins lymphoma is 60-200 times higher in HIV-positive subjects in comparison to the general population (4). The overexpression of the c-myc oncogene and the functional loss of the wild type p53 gene are considered as possible etiologic factors as well. Immunodeficient patients, particularly those with AIDS, and cardiac or renal transplant patients are more susceptible to developing BL. In our case, the patient was HIV-negative (8,9).

Conclusion

As is evident in the case presented, the clinical presentation of BL can be confused with a variety of other disorders in the oral cavity. Understanding the disease, its epidemiology, and including it in the differential diagnosis is essential for early detection of BL of the oral and maxillofacial area, in order to avoid delay and inappropriate treatment strategies.

Abstract
Burkitt's Lymphoma is an aggressive form of non-Hodgkin´s B-cell lymphoma. Here, we review the literature on Burkitt's Lymphoma and briefly summarize some clinical, etiological, genetic and histopathological aspects. We also present a case of Burkittt's lymphoma presenting as a maxillary swelling in an HIV-negative 35-year-old black man. The clinical presentation of Burkitt's Lymphoma can be confused with a variety of other disorders in the oral cavity. Understanding the disease, its epidemiology, and including it in the differential diagnosis is essential for early detection of Burkitt's lymphoma of the oral and maxillofacial area, in order to avoid delay and inappropriate treatment strategies.

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Burkitt Lymphoma; Lymphoma, B-Cell

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