ZNAČAJ PREVENTIVNE ULTRAZVUČNE DIJAGNOSTIKE U PRAVOVREMENOJ DETEKCIJI RETKIH I AGRESIVNIH TIREOIDNIH KARCINOMA – PRIKAZ SLUČAJA

PRIKAZ SLUČAJA

CASE REPORT

SIGNIFICANCE OF THE PREVENTIVE ULTRASOUND DIAGNOSTICS IN THE EARLY DETECTION OF RARE AND AGGRESSIVE THYROID CARCINOMAS – CASE REPORT

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SAŽETAK

Uvod: Medularni karcinom štitaste žlezde (MKŠ) je agresivan tumor udružen sa značajno lošijom prognozom u odnosu na druge tipove tireoidnog karcinoma. Dopler ultrazvučni pregled i adekvatna dijagnostika zasnovana na TIRADS (Thyroid Imaging Reporting and Data System) klasifikaciji suspektnih nodusa su neophodni.
Cilj: Ovaj prikaz slučaja naglašava značaj precizne ultrazvučne dijagnostike, presudne u ranoj detekciji i primeni adekvatnih hirurških postupaka u zbrinjavanju ovako agresivnih formi bolesti.
Prikaz slučaja: Prikazujemo pacijentkinju staru 31 godinu koja je ultrazvučno dijagnostikovana rutinskim sistematskim pregledom. Ultrazvučnim pregledom uočen je hipoehogeni, nejasno ograničen mikronodus dimenzija 5 mm x 4 mm x 3 mm, sa ehogenim fokusima lokalizovanim u centralnim zonama levog režnja štitaste žlezde (TIRADS 4, score 6). S obzirom na suspektno maligne ultrazvučne karakteristike, lokalizaciju mirkonodusa i sledstveno rađen povišen serumski nivo kalcitonina, postavljena je sumnja na mikromedularni karcinom. Nakon urađene kompletne tiroidektomije, dijagnoza je potvrđena histopatološkim pregledom. Histopatološka analiza pokazuje manji, beličast nodus (5 mm) u levom režnju, bez upadljive nekroze i bez amiloidnog sadržaja. Limfovaskularna invazija nije utvrđena, dok su mitoze retke. Stadijum tumorske bolesti je T1 (pTNM), bez udaljenih metastaza. Hiperplazija C ćelija je prisutna u okolini tumora. Imunohistohemijska analiza je pokazala pozitivnu reakciju na kalcitonin, hromogranin i mCEA. Proliferativni indeks je nizak (4%). Nakon hirurške intervencije nivo kalcitonina se normalizovano. Tri godine nakon operacije pacijentkinja je dobrog opšteg stanja, na redovnom praćenju. U međuvremenu se pacijentkinja ostvarila kao majka.
Zaključak: Rana detekcija i pravovremeni terapijski pristup u lečenju mikromedularnog karcinoma štitaste žlezde su vrlo značajni, s obzirom na vrlo agresivno biološko ponašanje ovih tumora. Adekvatan ultrazvučni pregled može značajno promeniti terapijski ishod i prognozu bolesti kod ovakvih pacijenata.
Ključne reči: ultrazvučna dijagnostika, mikronodus štitaste žlezde, mikromedularni karcinom

ABSTRACT

Introduction: Medullary thyroid carcinoma (MTC) is an aggressive tumor associated with a significantly poorer prognosis compared to other types of thyroid cancer. Doppler ultrasound and familiarity with the Thyroid Imaging Reporting and Data System (TIRADS) nodule classification are essential.
Objective: This case highlights the significance of precise ultrasound imaging, crucial for early detection and subsequent management of such aggressive disease.
Case report: We describe the case of a 31-year-old woman who underwent systemic ultrasound imaging. Upon ultrasound examination, a 5 mm x 4 mm x 3 mm hypoechoic, ill-defined solid nodule with echogenic foci (TIRADS 4, score 6) was identified in the mid portion of the left thyroid lobe. Given the suspicious ultrasound features, the location of the nodule, and the elevated serum calcitonin level, the micronodule raised concerns for malignancy, particularly suggesting medullary thyroid microcarcinoma. The patient underwent thyroidectomy, and histopathological analysis confirmed the diagnosis. The histopathology report described a small white nodule (5 mm) in the left lobe. There was no remarkable necrosis, and amyloid deposits were inconspicuous. Lymphovascular invasion was not observed, and mitoses were rare. The tumor stage was T1 (pTNM), and no distant metastases were found. C-cell hyperplasia was noted around the tumor. Immunohistochemical analysis showed positive reactions for calcitonin, chromogranin, and mCEA. The proliferative index was low, approximately 4%. After surgery, serum calcitonin levels decreased. Three years after the surgery, the patient is in good general condition and is under regular monitoring. In the meantime, the patient has become a mother.
Conclusion: Early detection and treatment of micro-MTC are crucial, as these tumors have the potential for aggressive behavior. Adequate ultrasound imaging assessment could significantly improve the prognosis and outcome for these patients.
Keywords: ultrasound imaging, thyroid nodule, micro-medullary carcinoma

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UVOD

Medularni karcinom štitaste žlezde (MKŠ) predstavlja redak tumor koji obuhvata oko 5% svih maligniteta štitaste žlezde. MKŠ je agresivan tumor i ima znatno nepovoljniju prognozu od drugih tipova karcinoma štitaste žlezde [1]. MKŠ je odgovoran za oko 13% smrtnih ishoda povezanih sa karcinomom štitaste žlezde, što ukazuje na njegovu izraženu kliničku agresivnost u poređenju sa folikularnim neoplazmama (FDN) [2]. Njegov potencijal za rano metastaziranje u regionalne limfne čvorove često dovodi do povišenog serumskog nivoa kalcitonina. Iako je potreba za limfadenektomijom u odsustvu palpabilne nodularne bolesti predmet debate, studije ukazuju na to da uspostavljanje normalnog serumskog nivoa kalcitonina korelira sa višom stopom preživljavanja. Integrisana procena ultrazvučnih i biohemijskih parametara pokazala se značajnom u predviđanju prognoze MKŠ-a [1,3].

Serumski kalcitonin predstavlja ključni tumorski marker, sa visokom specifičnošću za MKŠ [4]. Kod pacijenata koji puše ili koriste određene lekove, poput inhibitora protonske pumpe (IPP), mogu se javiti lažno pozitivni rezultati, što smanjuje specifičnost serumskog kalcitonina. U takvim slučajevima dijagnoza se zasniva na kontinuiranom porastu serumskog nivoa kalcitonina tokom vremena, uprkos prekidu upotrebe duvana i terapije inhibitorima protonske pumpe, u kombinaciji sa prisustvom suspektnog solitarnog mikronodusa u centralnoj oblasti gornjeg ili srednjeg dela režnja štitaste žlezde [1].

Mikro-MKŠ, koji se obično definiše kao tumor manji od 1 cm, uglavnom se javlja u kontekstu familijarnog MKŠ-a ili kao rezultat inicijative za sprovođenje skrininga nivoa kalcitonina. Ova studija prikazuje lečenje pacijenta sa sporadičnim mikro-MKŠ-om u odsustvu takvih programa skrininga [1,5].

Čvorići na štitastoj žlezdi često se otkrivaju slučajno tokom ultrazvučnih (UZ) pregleda vrata kod odraslih pacijenata. U takvim slučajevima neophodno je sveobuhvatno poznavanje ultrazvučnih karakteristika čvorova pri pregledu visokofrekventnim dopler ultrazvukom, kao i poznavanje klasifikacije čvorova prema TIRADS (Thyroid Imaging Reporting and Data System) sistemu [6,7]. Čvorovi na štitastoj žlezdi sa ultrazvučnim karakteristikama koje upućuju na malignitet, kao što su izražena hipoehogenost, nepravilne ivice, mikrokalcifikacije, „viši nego širi" oblik i povećana krutost pri elastografiji, zahtevaju aspiracionu biopsiju tankom iglom (FNAC), nakon čega sledi citološka procena prema Bethesda klasifikaciji iz 2010. godine, bez obzira na veličinu čvora. Pored toga, dopler ultrasonografskim pregledom mogu se otkriti dodatne suspektne karakteristike, uključujući dezorganizovane centralne krvne

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare tumor, accounting for 5% of thyroid malignancies. MTC is an aggressive tumor, associated with a significantly poorer prognosis compared to other types of thyroid cancer [1]. MTC is responsible for approximately 13% of deaths related to thyroid cancer, indicating its considerable clinical aggressiveness compared to follicular-derived neoplasms (FDN) [2]. Its potential to metastasize to regional lymph nodes early in its progression often results in elevated serum calcitonin levels. While the necessity of lymphadenectomy in the absence of palpable nodal disease sparks debate, studies have shown that successful normalization of serum calcitonin levels correlates with enhanced survival. A combined assessment of ultrasound and biochemical features is associated with the prognosis of MTC [1,3].

Serum calcitonin serves as a key tumor marker and is highly specific for MTC [4]. Patients who smoke or use certain medications, such as proton-pump inhibitors (PPIs), may induce false-positive results, thereby reducing the specificity of serum calcitonin. In such cases, diagnosis is based on a continuous rise in serum calcitonin levels over time, despite discontinuation of tobacco use and PPI therapy, combined with the presence of a suspicious solitary micronodule in the central region of the upper/mid thyroid lobe [1].

The concept of micro-MTC, typically defined as MTC measuring less than 1 cm, has predominantly emerged within familial MTC contexts or as a result of calcitonin screening initiatives. This study describes the management of patients with sporadic micro-MTC in the absence of such screening programs [1,5].

Thyroid nodules are commonly discovered incidentally during neck ultrasound (US) examinations in adults. In such instances, a comprehensive understanding of thyroid nodule characteristics on high-frequency Doppler ultrasound and familiarity with the Thyroid Imaging Reporting and Data System (TIRADS) nodule classification are essential [6,7]. Thyroid nodules with ultrasound features suggestive of malignancy, such as marked hypoechogenicity, irregular margins, microcalcifications, a taller-than-wide shape, and high stiffness on elastography, warrant fine-needle aspiration cytology (FNAC), followed by cytological evaluation according to the 2010 Bethesda classification, regardless of nodule size. Additionally, Doppler US evaluation may reveal supplementary suspicious features, including disorganized central vasculature and a high resistance index (RI > 0.75). MTC may also exhibit distinctive US Doppler features [1,8].

The natural history of MTC has been difficult to delineate due to its rarity. The significance of medullary

sudove i visok indeks otpora (RI > 0,75). MKŠ takođe može imati karakteristične ultrazvučne osobine [1,8].

Prirodni tok MKŠ-a je teško odrediti zbog njegove niske učestalosti. Klinički značaj medularnih mikrokarcinoma i dalje nije razjašnjen, iako se često otkrivaju, uglavnom u okviru programa skrininga nivoa kalcitonina. Nivoi serumskog kalcitonina iznad 100 pg/mL obično ukazuju na makro-MKŠ [1]. Ovaj nedostatak konsenzusa odnosi se i na klinički značaj i optimalno lečenje mikro-MKŠ-a, posebno kada je reč o sporadičnim i okultnim formama [1,2].

Ova studija ističe značaj preciznog ultrazvučnog skeniranja, koje je od ključnog značaja za rano otkrivanje i dalje lečenje, u cilju sprečavanja nepovoljne prognoze kod ove agresivne bolesti.

STUDIJA SLUČAJA

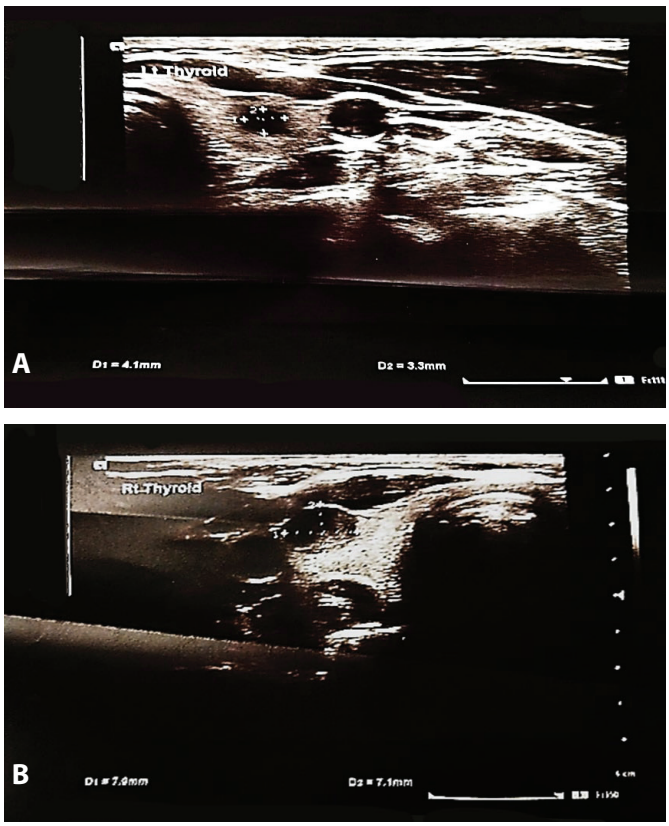
Prikazujemo slučaj 31-godišnje pacijentkinje koja je ultrazvučno dijagnostikovana rutinskim sistematskim pregledom. Ultrazvučnim pregledom uočen je hipoehogeni, nejasno ograničen nodus dimenzija 5 mm x

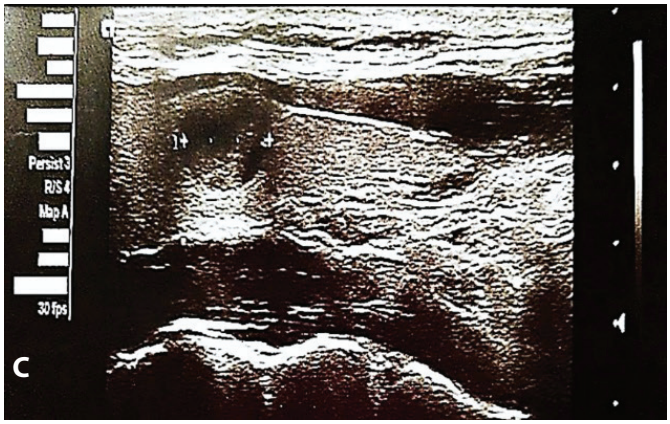
microcarcinomas remains elusive despite their frequent detection, often through calcitonin screening programs. Serum calcitonin levels above 100 pg/mL are generally indicative of macro-MTC [1]. This lack of consensus extends to the clinical significance and optimal management of micro-MTC, particularly within sporadic and occult settings [1,2].

This study highlights the significance of precise ultrasound imaging, crucial for early detection and further management, in order to prevent a poor prognosis for such an aggressive disease.

CASE REPORT

We describe a 31-year-old woman who underwent systemic ultrasound imaging. Upon ultrasound examination, a 5 mm x 4 mm x 3 mm hypoechoic ill-defined nodule with echogenic foci (TIRADS 4) was identified in the mid portion of the left thyroid lobe (Figure 1). Additionally, her serum calcitonin level was measured at 17.7 pg/mL. Serum calcitonin was repeated several times over a three-month period. Given the suspicious





Slika 1. Ultrazvučni pregled štitaste žlezde pacijenta. Ultrazvučni pregled štitaste žlezde prikazuje sumnjiv čvor u levom režnju. A i B. Mali hipoehogeni, solidni čvor veličine 5 mm sa ehogenim fokusima, prisutnom vaskularizacijom i nepravilnim marginama (TIRADS 4, skor 6), lociran u srednjem delu levog režnja štitaste žlezde. C. U kontralateralnom desnom režnju, anteriorno i kranijalno, prikazan je mešoviti, pretežno cistični čvor veličine 9 mm sa centralnom vaskularizacijom; za razliku od levog čvora, ima drugačiju ultrazvučnu sliku i ne pokazuje sumnjive karakteristike maligne lezije.

Figure 1. Ultrasound imaging of the patient's thyroid gland. Ultrasound examination of the thyroid gland detected a suspicious nodule in the left lobe. A. and B. Small hypoechoic, solid nodule (5mm) with echogenic foci, vascularization and irregular margins (TIRADS4, score 6) in the mid portion of the left thyroid lobe. C. In the contralateral right lobe, anterior and cranial, there was a mixed, predominantly cystic nodule measuring 9 mm with central vascularization. Unlike the left nodule, this lesion displayed a different imaging pattern and lacked suspicious malignant features

4 mm x 3 mm, sa ehogenim fokusima (TIRADS 4) lokalizovanim u centralnim zonama levog režnja štitaste žlezde (Slika 1). Pored toga, kod pacijentkinje je izmeren serumski nivo kalcitonina, koji je iznosio 17,7 pg/mL. Serumski kalcitonin je ponovo meren više puta tokom tromesečnog perioda. S obzirom na suspektne ultrazvučne karakteristike, lokalizaciju nodusa i povišen serumski nivo kalcitonina, mikronodus je ukazao na postojanje maligniteta, posebno imajući u vidu mikromedulrni karcinom.

Pacijentkinja je upućena u tercijarnu ustanovu radi dalje dijagnostike štitaste žlezde. Potom je podvrgnuta tireoidektomiji, a histopatološka analiza je potvrdila dijagnozu. Preoperativna biopsija kod pacijentkinje nije rađena. U histopatološkom izveštaju opisan je mali beličast nodus u levom režnju, prečnika 5 mm (Slika 2). Nije bilo upadljive nekroze i amiloidnog sadržaja. Limfovaskularna invazija nije utvrđena, dok su mitoze bile retke. Stadijum tumorske bolesti bio je T1 (pTNM). Status limfnih čvorova nije histopatološki procenjivan, a udaljene metastaze nisu pronađene. Oko tumora je uočena hiperplazija C-ćelija, dok je ostatak tkiva štitaste žlezde pokazivao stromalne promene.

Imunohistohemijska analiza je pokazala pozitivnu reakciju na kalcitonin, hromogranin i mCEA. Imunohistohemijsko bojenje na markere HBME, CD56, CK19 i galektin-3 bilo je negativno. S100 je bio prisutan u retkim, pojedinačnim ćelijama. Proliferativni indeks je bio nizak, približno 4%.

Pacijentkinja nije prijavila slična oboljenja niti genetsku predispoziciju u porodičnoj anamnezi. Nakon operacije, serumski nivo kalcitonina je opao. Genetska analiza nije otkrila specifične promene povezane sa detektovanim MKŠ-om, što ukazuje na sporadičnu formu bolesti.

Pacijentkinja je upućena na kliničko i radiološko praćenje, koje uključuje redovno merenje nivoa serumskog kalcitonina i detaljne kliničke preglede. Ultrazvučni pregledi se obavljaju na svakih šest meseci.

ultrasound features, the location of the nodule, and the elevated serum calcitonin level, the micronodule raised concerns for malignancy, particularly suggesting medullary thyroid microcarcinoma.

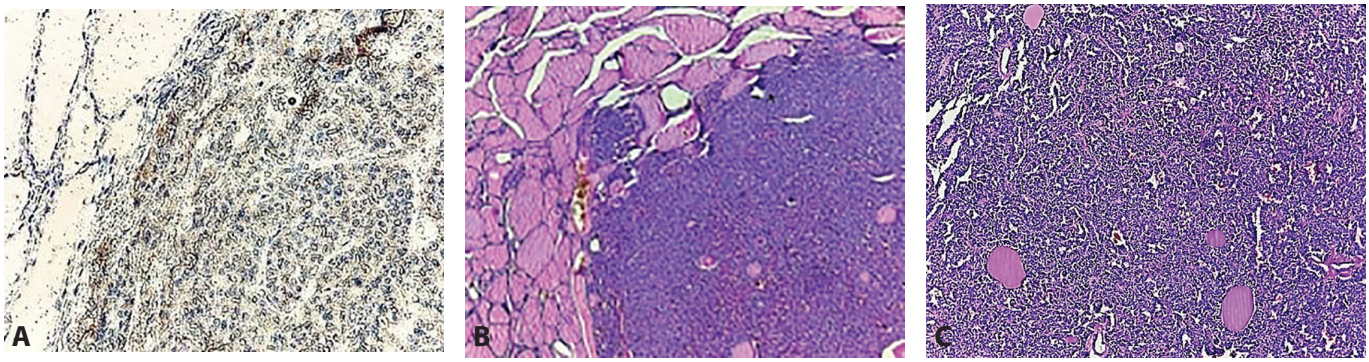
The patient was referred to a tertiary institution for further investigation of her thyroid gland. Subsequently, she underwent thyroidectomy, and histopathological analysis confirmed the diagnosis. The patient did not undergo a preoperative biopsy. The histopathology report described a small white nodule in the left lobe, with a diameter of 5 mm (Figure 2). There was no remarkable necrosis, and amyloid was inconspicuous. Lymphovascular invasion was not observed, and mitoses were rare. The tumor stage was T1 (pTNM). Lymph node status was not evaluated histopathologically, and no distant metastases were found. C-cell hyperplasia was observed around the tumor, and the rest of the thyroid tissue showed stromal changes.

Immunohistochemical analysis showed positive reactions for calcitonin, chromogranin, and mCEA. Negative staining was observed with HBME, CD56, CK19, and galectin-3. S100 was found in rare, single cells. The proliferative index was low, approximately 4%.

The patient did not report any similar disease or genetic inheritance in her family history. After surgery, serum calcitonin levels decreased. The genetic analysis performed did not reveal any specific alterations associated with the detected MTC, suggesting a sporadic form of the disease.

The patient was referred for clinical and imaging follow-up, which includes regular serum calcitonin measurements and thorough clinical examinations. Ultrasound examinations are performed every six months.

Three years after the surgery, the patient is in good general condition and is under regular monitoring. In the meantime, the patient has become a mother.



Slika 2. Histopatološki nalaz. Histopatološki prikaz mikromedularnog karcinoma štitaste žlezde (A. uvećanje x50) i (B. uvećanje x100). Imunohistohemijska analiza na kalcitonin pokazuje pozitivnu reakciju u neoplastičnim ćelijama (C. uvećanje x400)

Figure 2. Histopathology examination. Histopathology pattern of micromeddullary thyroid carcinoma (A. x50) and (B. x100). Immunohistochemical analysis with calcitonin shows positive reaction in neoplastic cells (C. x400)

Tri godine nakon operacije, pacijentkinja je u dobrom opštem stanju i njeno stanje se redovno prati. U međuvremenu, pacijentkinja je postala majka.

DISKUSIJA

Mikro-medularni karcinomi se često slučajno otkrivaju tokom preventivne tireoidektomije. Zahvaljujući napretku ultrazvučne tehnologije, sada je moguće otkriti manje noduse pre donošenja odluke o hirurškom tretmanu. Rano hirurško uklanjanje tumora značajno povećava šanse za izlečenje kod pacijenata sa mikro-MKŠ-om [2].

S obzirom na male dimenzije mikro-MKŠ-a, tokom kliničkog praćenja nisu zabeleženi slučajevi recidiva tumora niti udaljenih metastaza. Preovlađujuće mišljenje u literaturi ukazuje na to da je mikro-MKŠ povezan sa višim stopama izlečenja i nižim rizikom od metastaza i smrtnosti u poređenju sa većim tumorima, pri čemu samo retki slučajevi pokazuju klinički agresivno ponašanje [9]. I naši nalazi idu u prilog ovom mišljenju.

Pošto na prognozu MKŠ-a značajno utiču volumen tumora i stepen njegovog širenja, radiolozi moraju biti vešti u prepoznavanju specifičnih ultrazvučnih karakteristika koje su svojstvene MKŠ-u. Rana i precizna dijagnoza od ključnog je značaja za optimalno hirurško lečenje i dugoročne ishode kod pacijenata sa ovim agresivnim tumorom [1,8].

MKŠ se obično javlja u centralnoj oblasti gornjeg ili srednjeg dela režnja štitaste žlezde, gde su koncentrisane C (parafolikularne) ćelije. Radiolozi treba da obrate pažnju na prisustvo hiperehogenih tačkica na ultrazvučnim snimcima, koje mogu odgovarati depozitima amiloidnog sadržaja ili kalcifikacijama. Takvi nalazi treba da navedu radiologa da sprovede aspiracionu biopsiju tankom iglom (FNAC) radi daljeg ispitivanja [10]. S obzirom na povezanost MKŠ-a i multiple endokrine neoplazije (posebno RET mutacija), radiolozi treba posebno da obrate pažnju na eventualno uvećanje paratireoidnih žlezda koje se nalaze iza režnja štitaste žlezde, medijalno u odnosu na karotidne ovojnice vrata [1].

Iako su neki slučajevi MKŠ-a povezani sa multiplom endokrinom neoplazijom (MEN) tipa IIa ili IIb, većina ovih tumora nastaje sporadično. Tokom patohistološke analize uzoraka štitaste žlezde uzetih zbog sumnje na benigne bolesti ili ne-medularne karcinome štitaste žlezde, zabeleženo je otkrivanje malih (manjih od 1 cm), okultnih MKŠ-ova, poznatih kao mikro-MKŠ, kako kod pacijenata sa porodičnom istorijom MEN-a ili MKŠ-a, tako i kod onih bez takve istorije. Prognostičke implikacije i optimalno hirurško lečenje sporadičnih formi mikro-MKŠ-a i dalje nisu jasno definisani [1,11].

Većina slučajeva MKŠ-a ima sporadičnu formu i javljaju se nezavisno od porodične predispozicije. Međutim, do 25% slučajeva MKŠ-a povezano je sa jednim

DISCUSSION

Micro-medullary carcinomas are often detected incidentally during prophylactic thyroidectomy procedures. Advancements in ultrasound technology now enable the detection of smaller nodules before surgical decisions are made. Early resection offers a significant possibility of cure in micro-MTC cases [2].

Considering the small size of micro-MTC, no cases of tumor recurrence or distant metastases were observed during clinical follow-up. The prevailing notion in the literature indicates that micro-MTCs are associated with higher cure rates and a lower risk of metastases and mortality compared to larger tumors, with only rare cases exhibiting clinically aggressive behavior [9]. Our findings further support this notion.

Since the prognosis of MTC is strongly influenced by tumor volume and extent of spread, radiologists must be proficient in identifying specific imaging features characteristic of MTC. Early and accurate diagnosis is paramount for optimizing surgical management and long-term outcomes in patients with this aggressive tumor [1,8].

MTC typically originates in the upper or mid portion of the central thyroid lobe, where C (parafollicular) cells are concentrated. Radiologists should be alert to the presence of hyperechoic punctuations on ultrasound imaging, which may correspond to amyloid deposits or calcifications. Such findings should prompt the radiologist to perform a fine needle aspiration cytology (FNAC) for further evaluation [10]. Given the association between MTC and multiple endocrine neoplasia (especially RET mutations) radiologists should carefully evaluate for enlarged parathyroid glands situated posterior to the thyroid lobes, medial to the cervical carotid sheaths [1].

While some cases of MTC are associated with multiple endocrine neoplasia (MEN) types IIa or IIb, the majority arise sporadically. The discovery of small (less than 1 cm) occult MTCs, known as micro-MTCs, during pathological examination of thyroid specimens resected for benign conditions or non-MTC thyroid cancers, has been reported in both patients with and without familial histories of MEN or MTC. The prognostic implications and optimal surgical management of sporadic micro-MTC remain unclear [1,11].

The majority of MTC cases are sporadic, occurring without a familial predisposition. However, up to 25% of cases are associated with one of three familial syndromes: Multiple Endocrine Neoplasia type 2A (MEN2A), Multiple Endocrine Neoplasia type 2B (MEN2B), and Familial Medullary Thyroid Carcinoma (FMTC). These familial cases are attributed to germline gain-of-function autosomal-dominant mutations in the

od tri nasledna sindroma: multiplom endokrinom neoplazijom tipa 2A (MEN2A), multiplom endokrinom neoplazijom tipa 2B (MEN2B) i familijarnim medularnim karcinomom štitaste žlezde (FMTC). Ovi nasledni slučajevi se pripisuju germinativnim autozomno-dominantnim mutacijama sa sticanjem funkcije (gain-of-function) u protoonkogenu RET [2,5]. Germinativna RET K666N mutacija koja nastaje na jednom alelu povezuje se sa rizikom of dobijanja naslednog MKŠ-a, pri čemu se ekspresivnost menja u zavisnosti od starosti. Međutim, ove varijante pokazuju nižu penetrabilnost za druge tumore koji su karakteristični za MEN2 sindrom [12].

Sporadična forma MKŠ-a se obično javlja kao palpabilan nodus štitaste žlezde kod osoba u dobi između pete i šeste decenije života. Nasuprot tome, nasledna forma se javlja u mlađem uzrastu, a klinička slika varira u zavisnosti od pridruženog sindroma. Na primer, MEN2A karakteriše prisustvo feohromocitoma i hiperparatireoidizma, dok je MEN2B povezan sa pojavama kao što su feohromocitom, mukozni neuromi i Marfanov sindrom. Važno je napomenuti da se nasledna forma MKŠ-a često javlja multifokalno ili bilateralno i da je često povezana sa hiperplazijom C-ćelija [2,13,14].

Razlikovanje MKŠ-a od češćih maligniteta štitaste žlezde, kao što je papilarni karcinom štitaste žlezde (PTC), samo uz pomoć ultrazvučne dijagnostike može predstavljati izazov. Neke studije sugerišu da kombinovanje različitih TIRADS sistema skorovanja poboljšava dijagnostičku preciznost [15], dok su druge pokazale efikasnost modela radiomike u razlikovanju ovih entiteta [16]. Ultrazvučna procena vaskularizacije može pomoći pri razlikovanju MKŠ-a od benignih nodusa štitaste žlezde. MKŠ se odlikuje prepoznatljivom infiltrativnom razgranatom vaskularizacijom. Integrisanje ovih vaskularnih karakteristika u ultrazvučne sisteme za procenu rizika može poboljšati prepoznavanje MKŠ-a kod nodusa sa niskom do srednjom suspektnošću i omogućiti preciznije kliničko vođenje pacijenata [17]. Savremene metode snimanja MKŠ-a istakle su značaj jedinjenja usmerenog na CCK2 receptor (CCK2 R-Targeting Compound) [18].

Donošenje odluka o lečenju slučajno otkrivenog sporadičnog mikro-MKŠ-a predstavlja izazov, posebno kada je reč o hirurškom pristupu i zbrinjavanju metastaza koje su otkrivene biohemijskim ili radiološkim putem. U slučajevima u kojima je MKŠ dijagnostikovan pre operacije, rutinski se izvodi totalna tireoidektomija sa disekcijom limfnih čvorova u centralnom delu. Disekcija bočnih limfnih čvorova rezervisana je za slučajeve kod kojih postoji klinički značajna zahvaćenost nodusa [5].

Prethodna istraživanja ukazuju na povezanost manje agresivnog fenotipa sa manjim, slučajno otkrivenim tumorima. Važno je napomenuti da su vaskularna

RET proto-oncogene [2,5]. Monoallelic germline RET K666N mutations are associated with a risk of developing familial MTC, exhibiting age-dependent expressivity. However, these variants show low penetrance for other tumors typically seen in MEN2 syndromes [12].

Sporadic MTC typically presents with a palpable thyroid nodule in individuals aged between their 5th and 6th decades of life. In contrast, familial cases tend to occur at a younger age, and their presentation varies depending on the associated syndrome. For instance, MEN2A is characterized by the presence of pheochromocytoma and hyperparathyroidism, while MEN2B is associated with features such as pheochromocytoma, mucosal neuromas, and a marfanoid habitus. Importantly, familial MTC cases often present multifocally or bilaterally and are frequently associated with C-cell hyperplasia [2,13,14].

Differentiating MTC from more common thyroid malignancies such as papillary thyroid carcinoma (PTC) using ultrasound examination alone can be challenging. Some studies have suggested that combining various TIRADS scoring systems improves diagnostic accuracy [15], while others have demonstrated the effectiveness of radiomics models in distinguishing between these entities [16]. Evaluation of vascularity characteristics on ultrasound can assist in differentiating MTC from benign thyroid nodules. MTC is notably characterized by a distinctive penetrating branching vascular pattern. Integrating these vascular features into ultrasound-based risk stratification systems may enhance the identification of MTC among nodules with low to intermediate suspicion, thus facilitating more precise clinical management [17]. Novel imaging methods for MTC have highlighted the significance of CCK 2 R-Targeting Compound [18].

Navigating treatment decisions for incidentally discovered sporadic micro-MTC poses challenges, especially concerning the surgical approach and management of biochemical or radiologically detected metastatic disease. In cases with a preoperative diagnosis of MTC, total thyroidectomy with central compartment lymph node dissection is routinely performed. Lateral neck dissections are reserved for cases with clinically relevant nodal involvement [5].

Previous studies have described a correlation between a less aggressive phenotype and smaller, incidentally found tumors. Notably, only tumors larger than 0.5 cm exhibited evidence of vascular invasion or extrathyroidal extension. Desmoplastic reactions were also observed, with larger tumors more likely to exhibit such reactions. However, the relationship between desmoplasia, tumor size, and the presence of nodal metastases could not be conclusively established [1,5].

invazija i ekstratiroidna ekstenzija primećeni samo kod tumora većih od 0,5 cm. Uočene su i dezmoplastične reakcije, pri čemu su ovakve promene bile češće kod većih tumora. Ipak, nije bilo moguće sa sigurnošću utvrditi odnos između dezmoplazije, veličine tumora i prisustva limfnih metastaza [1,5]. Procena ekspresije Ki-67 predstavlja prediktivni histopatološki parametar koji se može koristiti zajedno sa ultrazvučnim karakteristikama za procenu agresivnosti MKŠ-a [19].

Medularni karcinom štitaste žlezde (MKŠ) predstavlja značajan klinički izazov jer pokazuje ograničenu osetljivost na hemioterapiju i radioterapiju. Shodno tome, osnovna strategija lečenja zasniva se prvenstveno na hirurškom odstranjivanju štitaste žlezde uz disekciju limfnih čvorova. Limfni čvorovi su zahvaćeni u značajnom broju slučajeva, naročito kod pacijenata sa uznapredovalim tumorima (klasifikovanim kao T3 i T4), što ukazuje na agresivnu prirodu ove maligne bolesti. Stoga je rana preoperativna dijagnostika ključna za planiranje lečenja, koje se obično sprovodi kombinovanjem preoperativne aspiracione biopsije tankom iglom i određivanjem nivoa serumskog kalcitonina [2,20].

Rutinska preventivna skrining dijagnostika MKŠ-a u opštoj populaciji prvenstveno se zasniva na određivanju nivoa serumskog kalcitonina, a ne na preventivnoj ultrazvučnoj dijagnostici. Ultrazvučna dijagnostika se obično razmatra kod pacijenata kod kojih su stalno povišene vrednosti kalcitonina. Uprkos niskoj učestalosti mikro-medularnog karcinoma štitaste žlezde i činjenici da ultrazvuk nije standardna metoda skrininga za ovu bolest, adekvatan i precizan inicijalni radiološki pregled može značajno uticati na klinički tok, posebno kada se bolest otkrije u ranoj fazi [10,21].

Preporučuje se da se preventivna tireoidektomija obavi do pete godine života ili ranije, naročito kod pacijenata sa povišenim serumskim kalcitoninom. Međutim, ispoljavanje i progresija bolesti unutar visokorizičnih grupa mogu značajno da variraju. Shodno tome, vreme izvođenja profilaktičke tireoidektomije više se ne određuje samo na osnovu genotipa, već na osnovu individualizovanih kliničkih parametara, sa posebnim naglaskom na koncentraciju serumskog kalcitonina [11].

ZAKLJUČAK

Iako je mikro-medularni karcinom štitaste žlezde redak patološki entitet i ultrazvuk nije standardna skrining metoda za njegovo otkrivanje, rano dijagnostikovanje je svakako od suštinskog značaja zbog potencijalno agresivnog ponašanja ovog tumora. Merenje nivoa serumskog kalcitonina i dalje predstavlja primarni alat za njegovo rano otkrivanje; međutim, kod pacijenata sa povišenim ili stalno rastućim nivoom kalcitonina, ciljana i precizna ultrazvučna dijagnostika može imati

Assessment of Ki-67 expression represents a predictive histopathological parameter that can be used alongside ultrasonographic features to evaluate the aggressiveness of MTC [19].

Medullary thyroid carcinoma (MTC) poses a significant clinical challenge as it exhibits limited responsiveness to chemotherapy and radiation therapy. Consequently, the cornerstone of its management primarily revolves around surgical excision of the thyroid gland with lymph node dissection. Lymph node involvement is prevalent in a considerable proportion of cases, particularly in patients with advanced tumors (T3–T4 tumors), highlighting the aggressive nature of this malignancy. Therefore, early preoperative diagnosis is crucial to facilitate appropriate treatment planning, typically achieved through preoperative fine needle aspiration analysis in conjunction with serum calcitonin measurements [2,20].

Routine preventive screening for MTC in the general population is primarily based on the measurement of serum calcitonin levels, rather than prophylactic ultrasound examination. Ultrasound imaging is typically considered in patients with persistently elevated calcitonin levels. Despite the low incidence of micro-medullary thyroid carcinoma and the fact that ultrasound is not a standard screening method for this disease, an adequate and precise primary radiological examination can significantly influence the clinical course, especially when the disease is detected at an early stage [10,21].

Prophylactic thyroidectomy is generally recommended by the age of five or earlier, especially in the presence of elevated serum calcitonin levels. However, the expression and progression of the disease within high risk categories can vary significantly. Consequently, the timing of prophylactic thyroidectomy is no longer based only on genotype, but rather on individualized clinical parameters, with particular emphasis on serum calcitonin concentrations [11].

CONCLUSION

Although micro-medullary thyroid carcinoma is a rare entity and ultrasound is not a standard screening method for its detection, early diagnosis remains essential due to the tumor's potential for aggressive behavior. Serum calcitonin measurement continues to be the primary tool for early detection; however, in patients with elevated or persistently rising calcitonin levels, targeted and precise ultrasound imaging can play a critical role. An accurate initial radiological assessment, particularly when the disease is detected at an early stage, can significantly influence the clinical course, improve prognosis, and contribute to better patient outcomes.

ključnu ulogu. Precizna inicijalna radiološka procena, naročito kada je bolest otkrivena u ranoj fazi, može značajno uticati na klinički tok, poboljšati prognozu i doprineti boljim ishodima lečenja.

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