

SKRINING MEDULARNOG KARCINOMA U OSOBA S ČVOROVIMA U ŠTITASTOJ ŽLEZDI

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SAŽETAK

Uvod/Cilj: Medularni karcinom štitaste žlezde (engl. *Medullary thyroid cancer* - MTC) je retka neuroendokrini neoplazma, koja nastaje iz parafolikularnih C ćelija, koje luče kalcitonin. Kalcitonin predstavlja osetljiv tumorski marker MTC, imajući u vidu da najveći broj obolelih ima povišene vrednosti istog. Ipak, ne postoji jedinstveni stav o upotrebi kalcitonina kao skrining testa za rano otkrivanje MTC kod osoba s čvorovima u štitastoj žlezdi. Cilj istraživanja je bio da se analizira mogućnost uvođenja kalcitonina kao skrining testa za rano otkrivanje MTC kroz prikaz jednog slučaja.

Prikaz bolesnika: U radu je prikazana pacijentkinja starosti 56 godina kojoj je prilikom sistematskog pregleda u desnom režnju štitne žlezde ustanovljeno prisustvo nodusa dijametra 10 x 8 mm i 5 x 4 mm. Laboratorijskom analizom utvrđene su blago povišene vrednosti kalcitonina (7,8 pg/mL, referentna vrednosti < 4,8 pg/mL). Test stimulacije kalcijumom bio je u referentnom rasponu, a vrednosti karcino-embrionalnog antigena uredne. Citološki pregled uzoraka aspiracione punkcije tankom iglom je odgovarao kategoriji T2 po *Bethesda* klasifikaciji (hronični limfocitni tireoiditis tipa Hašimoto). Na kontrolnom pregledu, sprovedenom posle 6 meseci, vrednosti kalcitonina nisu se značajno razlikovale u odnosu na prvobitne.

Zaključak: Kod prikazane pacijentkinje diskretno povišena koncentracija kalcitonina u serumu nije podrazumevala prisustvo MTC. Potrebna su dalja randomizovana klinička istraživanja kako bi se otklonile nesuglasice i utvrdile jedinstvene smernice za uvođenje kalcitonina kao skrining testa za MTC kod osoba sa čvorovima u štitastoj žlezdi.

Ključne reči: kalcitonin, medularni karcinom, štitasta žlezda, skrining

Uvod

Medularni karcinom štitne žlezde (engl. *Medullary thyroid cancer* - MTC) je retka neuroendokrini neoplazma (čini 4-10% svih karcinoma štitaste žlezde), koja nastaje iz parafolikularnih C ćelija koje luče kalcitonin (engl. *Calcitonin* - CTN) (1). Predominantno (75-80%) se javlja sporadično, ređe kao deo sindroma multiple endokrine neoplazije (engl. *Multiple endocrine neoplasia* - MEN) prvenstveno MEN IIA i MEN IIB i porodični MTC (engl. *Familial medullary thyroid cancer* - FMTC) (2).

Sporadični MTC ima vrhunac incidencije u petoj ili šestoj deceniji života (2). Inicijalno se manifestuje kao solitarni čvor u gornje dve trećine štitaste žlezde (2). U vreme postavljanja dijagnoze cervikalna limfadenopatija je prisutna u oko 50%

obolelih (1). Nasledni oblici se javljaju u mlađoj životnoj dobi (vrhunac incidencije u drugoj ili trećoj deceniji života) (2). Multicentrični su i bilateralni, varijabilne veličine (tumor manji od 1 cm ili tumor koji zauzima celu štitastu žlezdu i širi se na okolna meka tkiva) (1). Izolovani MTC-a ima relativno sporu progresiju (1). Nasledni oblik MTC-a ima agresivniji klinički tok, koji zavisi i od komorbiditeta (1).

Merenje CTN-a u krvi (bazalni CTN) primenjuje se kao skrining test, u diferencijalnoj dijagnozi, proceni odgovora na lečenje i za praćenje MTC (3-5). Osim toga, koristi se i test stimulacije penta-gastrinom i kalcijum glukonom (stimulisani CTN) (4,6). Iako pojedina Udruženja za štitastu žlezdu

CASE REPORT

SCREENING FOR MEDULLARY CARCINOMA IN PEOPLE WITH THYROID NODULES

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SUMMARY

Background/Aim: Medullary thyroid cancer (MTC) is a rare neuroendocrine neoplasm, which arises from parafollicular C cells, which secrete calcitonin. Calcitonin is a sensitive tumor marker of MTC, bearing in mind that the majority of patients have elevated values of it. However, there is no consensus on the use of calcitonin as a screening test for the early detection of MTC in individuals with thyroid nodules. The aim of the research was to analyze the possibility of introducing calcitonin as a screening test for the early detection of MTC through a case report.

Case report: The paper presents a 56-year-old female patient who, during a systematic examination, was found to have nodules with a diameter of 10 x 8 mm and 5 x 4 mm in the right lobe of the thyroid gland. Laboratory analysis revealed slightly elevated calcitonin values (7.8 pg/mL, reference values < 4.8 pg/mL). The calcium stimulation test was within the reference range, and the carcino-embryonic antigen values were normal. Cytological examination of fine-needle aspiration puncture samples corresponded to category T2 according to the Bethesda classification (Chronic lymphocytic thyroiditis of the Hashimoto type). At the control examination, carried out after 6 months, calcitonin values did not differ significantly compared to the original ones.

Conclusion: In the presented patient, the discreetly elevated concentration of calcitonin in the serum did not imply the presence of MTC. Further randomized clinical trials are needed to resolve controversies and establish uniform guidelines for the introduction of calcitonin as a screening test for MTC in individuals with thyroid nodules.

Key words: calcitonin, medullary carcinoma, thyroid gland, screening

Introduction

Medullary thyroid cancer (MTC) is a rare neuroendocrine neoplasm (accounts for 4 to 10% of all thyroid cancers), which arises from parafollicular C cells that secrete calcitonin (CTN) (1). Predominantly (75-80%) it occurs sporadically, less often as part of multiple neuroendocrine neoplasia (MEN), primarily MEN IIA and MEN IIB and familial medullary thyroid cancer (FMTC) (2).

Sporadic MTC has a peak incidence in the fifth or sixth decade of life (2). It initially manifests as a solitary nodule in the upper two-thirds of the thyroid gland (2). At the time of diagnosis, cervical lymphadenopathy is present in about 50% of patients (1). Hereditary forms occur at a younger age (peak incidence in the second or third decade of

life) (2). They are multicentric and bilateral, variable in size (a tumor smaller than 1 cm or a tumor that occupies the entire thyroid gland and spreads to the surrounding soft tissues) (1). Isolated MTC has a relatively slow progression (1). The hereditary form of MTC has a more aggressive clinical course, which also depends on comorbidities (1).

The measurement of CTN in the blood (basal CTN) is used as a screening test in a differential diagnosis, in the evaluation of response to treatment and for monitoring MTC (3-5). In addition, a stimulation test with pentagastrin and calcium gluconate (stimulated CTN) is also used (4,6). Although some Thyroid Associations recommend the use of CTN as a screening test for

preporučuju upotrebu CTN-a kao skrining testa za MTC kod osoba s čvorovima u štitastoj žlezdi, njegova vrednost još uvek nije potpuno razjašnjena (6). Cilj istraživanja je bio da se analizira mogućnost uvođenja kalcitonina kao skrining testa za rano otkrivanje MTC kroz prikaz jednog slučaja.

Prikaz slučaja

Prikom sistematskog pregleda pacijentkinje starosti 56 godina u desnom režnju štitaste žlezde ustanovljeno je prisustvo nodusa dijametra 10 x 8 mm i 5 x 4 mm. Pacijentkinja je dobrog opšteg zdravlja i do sada nije imala bilo kakve tegobe koje bi ukazivale na oboljenje štitaste žlezde. Negira bolesti od značaja za hereditet. Nakon laboratorijske obrade utvrđuju se blago povišene vrednosti kalcitonina (7,8 pg/mL, referentna vrednosti < 4,8 pg/mL) i snižene vrednosti slobodnog tiroksina (10,1 pmol/L, referentne vrednosti 12,00-22,00 pmol/L). Vrednosti tireostimulirajućeg hormona, slobodnog tiroksina i slobodnog trijodotironina su bile u referentnom rasponu. Pacijentkinja se upućuje specijalisti nuklearne medicine koji indikuje test stimulacije kalcijumom i određivanje vrednosti karcino-embrionalnog antigena. Test stimulacije kalcijumom nije ukazivao na prisustvo MTC, vrednosti karcino-embrionalnog antigena su bile uredne. Specijalista nuklearne medicine uradio je i aspiracionu punkciju tankom iglom (engl. *Fine Needle Aspiration Biopsy* - FNA). Citološki pregled uzoraka FNA je odgovarao kategoriji T2 po *Bethesda* klasifikaciji (Hronični limfocitni tireoditis tipa Hašimoto). Uključuje se supstituciona terapija levotiroksin natrijum. Na kontrolnom pregledu posle 6 meseci vrednosti tiroksina bile su u referentnom rasponu, dok se vrednosti kalcitoina nisu razlikovale od prvobitnih. Dimenzije nodusa ostale su nepromenjene.

Diskusija

Ovaj prikaz slučaja ukazuje na činjenicu da diskretno povišene vrednosti kalcitonina u serumu pacijentkinje nisu podrazumevale prisustvo MTC. Potrebna su dalja istraživanja kako bi se otklonile nesuglasice i utvrdile jedinstvene smernice za primenu CTN kao skrining testa za MTC u osoba s čvorovima u štitastoj žlezdi.

CTN je polipeptidni hormon izgrađen od 32 aminokiseline kojeg uglavnom proizvode parafolikularne C ćelije štitaste žlezde (3). Predstavlja

osetljiv tumorski marker MTC-a, jer najveći broj obolelih od MTC-a imaju povišene vrednosti ovog polipeptidnog hormona (7). Ipak, ne postoji jedinstveni stav o upotrebi kalcitonina za rano otkrivanje (skrining) MTC-a u osoba s čvorovima u štitastoj žlezdi (8).

Rutinsko merenje CTN-a može značajno poboljšati stopu preživljavanja i smanjiti troškove zdravstvene zaštite obolelih osoba (9). Nadalje, verodostojnost ultrazvučnog TI-RADS (od engl. *European Thyroid Imaging Reporting and Data System*) sistema stratifikacije rizika novootkrivenih čvorova u štitastoj žlezdi je suboptimalna (9). Takođe, citološki pregled uzoraka FNA prepoznaje najveći deo papilarnog karcinoma štitaste žlezde, ali samo više od polovine MTC-a (9).

Postoji nekoliko argumenata koji se protive rutinskom merenju CTN-a. Prvo, ne postoji međunarodni konsenzus o isplativosti ovog skrining testa (9,10), jer se primenjuje za otkrivanje retkog malignoma. Prevalencija MTC u osoba s čvorovima u štitastoj žlezdi iznosi između 0,11% i 0,85%, s medijanom od 0,32% (9). Takođe, približno polovina MTC identifikovanih rutinskim merenjem CTN su okultni MTC (10). Postoji mišljenje da okultni MTC imaju nizak maligni potencijal, kao i da nikada ne evoluiraju u veći i agresivniji tumor (10). Prevalencija okultnog MTC-a, na osnovu podataka studija baziranih na autopsijama, je oko 0,14% (6).

Osim toga, eminentni autori navode rizik od lažno pozitivnih i lažno negativnih rezultata (10). Naime, vrednosti serumskog CTN-a mogu se meriti s radio-imuno testom - (engl. *Radioimmunoassay* - RIA), imuno-radiometrijskim testom (engl. *Immunoradiometry assay* - IRMA) i imuno-hemiluminescentnim testom (engl. *Immunochemiluminescent assay* - ICMA) (11). RIA test identifikuje monomerni i dimerni oblik kalcitonina, kao i njegove prekursore (11). S druge strane, IRMA i ICMA test identifikuju zreli, monomerni oblik CTN (11). IRMA i ICMA test omogućavaju stvaranje „sendviča“ od antitela za hvatanje, epitopa CTN i signalnih antitela, ostavljajući iza sebe višak nevezanih signalnih antitela (7,12). Izvode se u jednom ili dva koraka sa monoklonskim ili monoklonskim i poliklonskim antitelima (7,12). Lažno pozitivni rezultati mogu nastati kao posledica visokih vrednosti uree, kreatinina i vitamina C u serumu prilikom upotreba RIA testa, kao i umrežavanja poliklonskih antitela ukoliko se primenjuje analiza u jednom koraku (7,12). Lažno

MTC in persons with nodules in the thyroid gland, its value has not been completely clarified yet (6). The aim of the study was to analyze the possibility of introducing calcitonin as a screening test for the early detection of MTC through a case report.

Case report

During a systematic examination of a 56-year-old female patient, the presence of nodules with a diameter of 10 x 8 mm and 5 x 4 mm was observed in the right lobe of the thyroid gland. The patient's general health status was good and she had not had any complaints that would indicate thyroid disease. She denied diseases of importance for heredity. After laboratory analysis, slightly elevated calcitonin values were found (7.8 pg/mL, reference values < 4.8 pg/mL), as well as lower values of free thyroxine (10.1 pmol/L, reference values 12.00-22.00 pmol/L). The values of thyroid stimulating hormone, free thyroxine and free triiodothyronine were within the reference range. The patient was referred to a nuclear medicine specialist who indicated a calcium stimulation test and the determination of carcino-embryonic antigen value. A calcium stimulation test did not indicate the presence of MTC, while the values of carcino-embryonic antigen were within a normal range. A nuclear medicine specialist performed a fine needle aspiration biopsy (FNA). The cytological examination of FNA samples corresponded to T2 category according to Bethesda classification (chronic lymphocytic thyroiditis or Hashimoto's disease). The substitution therapy levothyroxine sodium was prescribed. At the control examination after six months, thyroxine values were within a normal range, while calcitonin values did not differ from original values. The dimensions of nodules remained unchanged.

Discussion

This case report points to the fact that slightly elevated calcitonin values in the patient's serum did not imply the presence of MTC. Further research is needed to resolve controversies and establish uniform guidelines for the use of CTN as a screening test in persons with thyroid nodules.

CTN is a polypeptide hormone made of 32 amino acids, which is mainly produced by parafollicular C cells of the thyroid gland (3). It represents a sensitive tumor marker of MTC, because most of the patients with MTC have

elevated values of this polypeptide hormone (7). However, there is no uniform attitude towards the use of calcitonin for the early detection (screening) of MTC in persons with thyroid nodules (8).

Routine measurements of CTN can significantly improve the survival rate and reduce the costs of health care of patients (9). Furthermore, the reliability of the ultrasound TI RADS (European Thyroid Imaging Reporting and Data System) risk stratification system for newly detected thyroid nodules is suboptimal (9). Also, the cytological examination of FNA samples recognizes the majority of papillary carcinomas of the thyroid gland, but only more than half of MTCs (9).

There are several arguments against routine CTN measurement. First, there is no international consensus on the cost-effectiveness of this screening test (9,10), because it is applied for the detection of rare malignancy. The prevalence of MTC in persons with thyroid nodules ranges between 0.11% and 0.85%, with the median prevalence of 0.32% (9). Also, approximately half of MTCs identified by routine CTN measurement are occult MTCs (10). There is an opinion that occult MTCs have a low malignant potential, and that they never evolve into a larger and more aggressive tumor (10). The prevalence of occult MTC, according to the studies based on autopsies, is about 0.14% (6).

In addition, eminent authors state the risk of false positive and false negative results (10). Namely, the values of serum CTN can be measured by radioimmunoassay (RIA), immunoradiometry assay (IRMA) and immunochemiluminiscent assay (ICMA) (11). The RIA assay identifies the monomer and dimer forms of calcitonin, as well as its precursors (11). On the other hand, the IRMA and ISMA assays identify the mature, monomer form of CTN (11). The IRMA and ICMA assays enable the creation of a "sandwich" made of capture antibodies, epitopes of CTN and signaling antibodies, leaving behind the excess of unbound signaling antibodies (7,12). They are conducted in one or two steps with monoclonal or monoclonal and polyclonal antibodies (7,12). False positive results may occur as a consequence of high values of urea, creatinine and vitamin C in the serum when using the RIA assay, as well as the crosslinking of polyclonal antibodies when the analysis is administered in one step (7-12). A false negative result may cause a "high-dose hook" effect (7,12). One should know that in case of extremely high

negativan rezultat može uzrokovati „efekat kuke” (engl. kao „*high dose hook*”) (7,12). Treba znati da su prilikom ekstremno visoke koncentracije kalcitonina u analizi u jednom koraku sva antitela (uključujući i signalna antitela) zasićena epitopima što sprečava stvaranje sendviča (7,12). Veoma retko „blokirajuća” poliklonska antitela prilikom analize u jednom koraku mogu proizvesti lažno niske vrednosti CTN-a (7).

Sekundarna hiperplazija C ćelija, prisutna u bolestima štitaste žlezde (hronični tiroiditis, papilarni ili folikularni karcinom štitaste žlezde) i drugim bolestima (terminalna bubrežna insuficijencija, hiperparatireoidizam i hipergastrinemija) uzrokuje porast vrednosti serumskog CTN-a (10,13). Nekoliko vrsta neuroendokrinih tumora uključujući paragangliom, feohromocitom, vipom, inzulinom, karcinoid želuca i mikrocelularni tumor pluća može ektopično lučiti kalcitonin (6). Treba naglasiti da neuroendokrini tumori uglavnom proizvode manje CTN-a po gramu tkiva od MTC-a i ne povećavaju svoje izlučivanje CTN-a prilikom stimulacijskog testiranja (10).

Kontinuirana primena inhibitora protonske pumpe u periodu od 2 do 4 meseca povećava koncentraciju CTN-a u serumu (11). Reč je o lekovima koji uzrokuju stalnu stimulaciju gastrinskih ćelija antruma želuca i hipersekreciju gastrina (11). Osim toga, povećano izlučivanje CTN-a uzrokuju glukokortikosteroidi, beta blokatori, antagonisti peptida srodnog kalcitoninu, glukagon, enteroglu-kagon i pankreozimin (10,11).

S kliničkog aspekta, nepostojanje fiksnog praga bazalnog i stimulanog CTN u identifikovanju ili isključivanju MTC-a sprečava univerzalno prihvaćanje skrininga kod osoba s čvorovima u štitastoj žlezdi

(9,10). Iako smernice preporučuju uspostavljanje vlastitih graničnih vrednosti bazalnog i stimulanog CTN-a u svakoj laboratoriji, postojanje različitih raspona uveliko pridonosi navedenim poteškoćama (10). Nadalje, vrednosti CTN-a variraju u zavisnosti od individualnih karakteristika i stila života osobe (9-11). Muškarci imaju dvostruko više C ćelija i posledično više vrednosti CTN-a (<8,5 pg/ml) u odnosu na žene (<5 pg/ml) (11). Više vrednosti CTN-a utvrđene su u dece i osoba mlađe životne dobi (10,11). U prisustvu ograničenih informacija treba biti oprezan u definisanju graničnih vrednosti u dece uzrasta < 3 godine (10,11). Vrednosti CTN su povišene u pušača (10,11).

Osim toga, test stimulacije pentagastrinom je neophodno tumačiti ne samo kao apsolutnu vrednost, već i u odnosu na bazalnu vrednost CTN-a i, što je važnije, stepen povećanja CTN-a nakon podražaja (10). MTC predominantno podrazumeva minimalno povećanje od 160% (10). Rezultati dosadašnjih istraživanja o tumačenju i daljem postupanju u odnosu na vrednosti bazalnog i stimulanog CTN-a prikazani su u tabeli 1 (10,11).

CTN negativan MTC je iznimno redak (u literaturi je opisano 49 slučajeva CTN negativnih MTC-a) (14). Iako patofiziologija CTN negativnog MTC-a još uvek nije utvrđena, kao mogući uzroci navode se izmenjeni mehanizam sekrecije C ćelija, proizvodnja aberantnih prekursora CTN-a, koje ne prepoznaju testna antitela, ektopično poreklo timusa i „efekat kuke” (14).

U Sjedinjenim Američkim Državama i Evropi postoji ograničena dostupnost pentagastrina, koji se smatra najboljim testom stimulacije CTN-a (10).

Retrospektivno istraživanje grupe autora iz Nemačke među 12.984 osoba s čvorovima u štitas-

Tabela 1. Tumačenje i indikacije u odnosu na vrednosti bazalnog i stimulanog kalcitonina (adaptirano prema referencama 10 i 11)

Tumačenje		Indikacija
Bazalni kalcitonin		
≤ 10–20 pg/ml	Normalan	–
20–50 pg/ml	Nizak rizik od medularnog karcinoma štitaste žlezde (MTC)	Test stimulacije pentagastrinom/kalcijumom glukonatom
50-100 pg/ml	Umjeren rizik od MTC	Test stimulacije pentagastrinom/kalcijumom glukonatom
>100 pg/ml	Izuzetno visok rizik od MTC	Operativni zahvat
Test stimulacije pentagastrinom/ kalcijum glukonatom		
< 30–50 pg/ml	Normalan	–
50-100 pg/ml	Izuzetno visok rizik od hiperplazija C ćelija	Operativni zahvat
> 100 pg/ml	Izuzetno visok rizik od MTC	Operativni zahvat

concentration of calcitonin in one-step analysis, all antibodies (including the signaling antibodies) are saturated with epitopes, which prevents the creation of the sandwich (7,12). Very rarely, “blocking” polyclonal antibodies during one-step analysis can produce false low values of CTN (7).

The secondary hyperplasia of C cells, present in diseases of the thyroid gland (chronic thyroiditis, papillary or follicular thyroid carcinoma) and other diseases (terminal renal failure, hyperparathyroidism and hypergastrinemia) causes an increase in serum CTN values (10,13). Several types of neuroendocrine tumors including paraganglioma, pheochromocytoma, vipoma, insulinoma, gastric carcinoid tumors and microcellular lung cancer can ectopically secrete calcitonin (6). It should be emphasized that neuroendocrine tumors usually produce less CTN per gram of tissue in comparison to MTC and they do not increase their CTN secretion during stimulation testing (10).

A continuous application of proton pump inhibitors in the period of 2 to 4 months increases the concentration of CTN in the serum (11). It is a drug that causes a constant stimulation of gastrin cells of the gastric antrum and hypersecretion of gastrin (11). In addition, the increased secretion of CTN is caused by glucocorticosteroids, beta blockers, calcitonin gene-related peptide antagonists, glucagon, enteroglucagon and pancreozymin (10,11).

From the clinical point of view, the lack of the fixed threshold of basal and stimulated CTN in identifying or excluding MTC prevents the universal acceptance of screening among patients with thyroid nodules (9,10). Although the guidelines

recommend that each laboratory should establish its own threshold values for basal and stimulated CTN, the existence of different ranges greatly contributes to the above mentioned difficulties (10). Furthermore, CTN values vary depending on the individual characteristics and lifestyle of a person (9-11). Men have twice as many C cells and consequently higher values of CTN (<8.5 pg/ml) in comparison to women (<5 pg/ml) (11). Higher CTN values were found in children and younger persons (10,11). Due to the limited information, one should be careful when defining the reference values in children aged <3 years (10,11). CTN values are higher in smokers (10,11).

In addition, the pentagastrin stimulation test should be interpreted not only as an absolute value, but also in relation to the basal value of CTN, and what is more important, the degree of increase of CTN after stimulation (10). MTC predominantly implies the minimum increase of 160% (10). The results of previous studies on the interpretation and further activities in relation to the values of basal and stimulated CTN are shown in Table 1 (10,11).

CTN-negative MTC is extremely rare (49 cases of CTN-negative MTCs have been described in the literature) (14). Although the pathophysiology of CTN-negative MTC has not been established yet, possible causes included an altered mechanism of C cell secretion, production of aberrant CTN precursors, which are not recognized by the test antibodies, the ectopic origin of the thymus, and the “hook” effect (14).

In the United States of America and Europe, there is the limited availability of pentagastrin, which is considered to be the best CTN stimulation test (10).

Table 1. Interpretation and indications according to the values of basal and stimulated calcitonin (adapted based on references 10 and 11)

Interpretation		Indication
Basal calcitonin		
≤ 10–20 pg/ml	Normal	–
20–50 pg/ml	Low risk of medullary thyroid cancer (MTC)	Pentagastrin/calcium gluconate stimulation test
50-100 pg/ml	Moderate risk of MTC	Pentagastrin/ calcium gluconate stimulation test
>100 pg/ml	Extremely high risk of MTC	Surgical procedure
Pentagastrin/calcium gluconate stimulation test		
< 30–50 pg/ml	Normal	–
50-100 pg/ml	Extremely high risk of C cells hyperplasia	Surgical procedure
> 100 pg/ml	Extremely high risk of MTC	Surgical procedure

toj žlezdi preporučilo je skrining MTN-a u prisustvu i vrlo malih čvorova štitaste žlezde, nezavisno od ultrazvučnog izgleda (15). Testovi stimulacije pentagastrinom i kalcijum glukonatom nisu identifikovani kao superiorni u odnosu na bazalni CTN (15). U rutinskom merenju CTN-a u 5.817 osoba s čvorovima u štitastoj žlezdi, grupa istraživača u Italiji je bazalni CTN opisala kao vrlo osetljiv test u ranoj dijagnozi MTC-a, iako su u većini slučajeva bili potrebni potvrdni testovi stimulacije pentagastrinom (16). U istraživanju grupe autora u Sjedinjenim Američkim Državama, utvrđena je isplativost skrininga MTN-a u osoba s čvorovima u štitastoj žlezdi (sa odnosom troškova i koristi koji odgovara kolonoskopkom i mamografskom skriningu) (17). Metaanaliza sedamnaest studija sa ukupno 74.407 učesnika, autora iz Nemačke, ustanovila je da i bazalni CTN i kombinacija bazalnog i petagastrinom stimuliranog CTN-a imaju visoku osetljivost i specifičnost u otkrivanju MTC-a (7). Međutim, u osoba s intermedijarnim vrednostima CTN-a (bazalni CTN u žena < 30 pg/mL, u muškaraca < 60 pg/mL) treba razmotriti praćenje obolelih (strategija čekanja) kako bi se izbegli prekomerni operativni zahvati (7).

Test stimulacije kalcijum glukonatom nije preporučan kao skrining test za MTC (7). Pregled 16 kohortnih (retrospektivnih i prospektivnih) studija sa ukupno 72.368 učesnika, grupe autora iz Holandije, nije podržao dovoljno dokaza za sprovođenje skrininga MTN-a u osoba s čvorovima u štitastoj žlezdi (5). Kao alternativu autori predlažu merenje CTN-a u osoba s suspektnom kliničkom slikom, neodređenim nalazom FNA ili oboje (5).

Preporuke strukovnih udruženja o skriningu MTN nisu univerzalne (18,19). Evropsko udruženje za štitastu žlezdu (engl. *European Thyroid Association*, ETA) je, 2006. godine, preporučilo skrining MTC-a u osoba s novootkrivenim čvorovima u štitastoj žlezdi (12). Smernice Američkog udruženje za štitastu žlezdu (engl. *American Thyroid Association*, ATA), Američkog udruženja kliničkih endokrinologa (engl. *American Association of Clinical Endocrinologists*, AACE), Američkog društva endokrinologa (engl. *American College of Endocrinology*, ACE) i Italijanskog društva kliničkih endokrinologa (engl. *Italian Association of Clinical Endocrinologists*, AME) su neodređene po navedenom pitanju (18).

Zaključak

U prikazanom slučaju diskretno povišene vrednosti CTN u serumu nisu ukazivale na postojanje MTC-a. Potrebna su dalja randomizirana klinička istraživanja kako bi se otklonile nesuglasice i utvrdile jedinstvene smernice za primenu MTC-a, kao skrining testa, u osoba s čvorovima u štitastoj žlezdi. MTC je retka i potencijalno vrlo agresivna neuroendokrina neoplazma, predominantno ukoliko se dijagnoza postavi u uznapredovalim stadijumima bolesti. Zbog toga je neophodno sagledati sve prednosti i nedostatke da bi se merenje CTN-a, kao skrining test, koristilo u cilju ranog otkrivanja MTC-a u osoba s čvorovima u štitastoj žlezdi.

Konflikt interesa

Autorka je izjavila da nema konflikta interesa.

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A retrospective study by a group of authors from Germany conducted among 12,984 persons with thyroid nodules recommended screening for MTC even in case of very small thyroid nodules, regardless of their ultrasound appearance (15). Stimulation tests using pentagastrin and calcium gluconate were not identified as superior in relation to basal CTN (15). In the routine measurement of CTN in 5,817 persons with thyroid nodules, a group of researchers in Italy described basal CTN as a very sensitive test in the early diagnosis of MTC, although confirmatory pentagastrin stimulation tests were necessary in most cases (16). In a study by a group of authors in the United States of America, the cost-effectiveness of screening for MTC in persons with thyroid nodules was established (with a cost-benefit ratio which corresponds to colonoscopy and mammography screening) (17). A meta-analysis of seventeen studies by authors from Germany with a total of 74,407 participants found that both basal CTN and the combination of basal and pentagastrin-stimulated CTN have high sensitivity and specificity in detecting MTC (7). However, in persons with intermediate CTN values (basal CTN in women < 30 pg/mL, in men < 60 pg/mL), the follow-up of patients (waiting strategy) should be considered in order to avoid excessive surgical procedures (7). The calcium gluconate stimulation test is not recommended as a screening test for MTC (7). A review of 16 cohort studies (retrospective and prospective) with a total of 72,368 participants, by a group of authors from the Netherlands, did not support sufficient evidence for the implementation of screening for MTC in persons with thyroid nodules (5). As an alternative, the authors suggest the measurement of CTN in persons with the suspicious clinical picture, indeterminate findings of FNA or both (5).

The recommendations of professional associations about MTC screening are not universal (18,19). In 2006, the European Thyroid Association (ETA) recommended screening for MTC in persons with newly discovered thyroid nodules (12). The Guidelines of the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE) and the Italian Association of Clinical Endocrinologists (AME) are vague about the above mentioned question (18).

Conclusion

In the presented case report, discreetly elevated CTN values in the serum did not indicate the existence of MTC. Further randomized clinical trials are needed to resolve the dispute and establish the uniform guidelines for the use of CTN, as a screening test, in persons with thyroid nodules. MTC is a rare and potentially very aggressive neuroendocrine neoplasm, predominantly if the diagnosis is established at advanced stages of the disease. Therefore, it is necessary to consider all the advantages and disadvantages in order to use CTN measurements as a screening test aimed at early detecting of MTC in persons with thyroid nodules.

Competing interests

The author declared no competing interests.

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