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VELIKI CISTADENOM JAJNIKA PRIKRIVEN GOJAZNOŠĆU KOD PACIJENTKINJE SA GREJVSOVOM HIPERTIREOZOM

Sažetak: Tumori jajnika predstavljaju čest entitet u praksi. Tumorske mase jajnika dijametra preko 20 cm nazivaju se ogromnim tumorima jajnika. Njihova učestalost je mala, jer se većina slučajeva dijagnostikuje rano tokom rutinskih ginekoloških pregleda ili se uoče kao uzgredan nalaz. Pacijentkinja starosti 34 godine hospitalizovana je na Klinici za endokrinologiju radi započinjanja redukcije telesne mase (TM) primenom dijetetskog režima i nastavka lečenja hipertireoze. Pacijentkinja je dobila u TM oko 70 kg od 2019. godine, tokom koje joj je postavljena i dijagnoza hipertireoze. U septembru 2022. godine operisana štitasta žlezda (izvađen desni režanj i istmus); PH nalaz: struma colloides cystica partim hyperplastica gl. thyreoideae. Kao glavne tegobe na prijemu navodi osećaj pritiska u abdomenu i nedostatak vazduha. U objektivnom nalazu pacijentkinja morbidno gojazna (ITM 62 kg/m^2). Na inicijalnom i ponovljenom UZ abdomena viđena dobro ograničena potkožna tečna kolekcija promera oko 240 mm, koja na prednjem delu trbušnog zida pravi celulitis. Ginekološkim pregledom iza i iznad uterusa uočena anehogena formacija promera 110x80 mm. Urađen CT abdomena bez iv kontrasta: u projekciji desnih adneksa uočava se per magna cistična ekspanzivna TU promena dijametra 318x380x242 mm oštrih kontura, ispunjena seroznim tečnim sadržajem i okružena kapsulom (dif dg. cistadenom desnog jajnika). Pacijenktinja predstavljena konzilijumu na Institutu za onkologiju i radiologiju Srbije na kome je odlučeno da se u jednom aktu operativno ukloni tumor desnog jajnika i preostali levi režanj štitaste žlezde. PH nalaz: 1. cystadenoma mucinosum ovarii; 2. struma colloides micro et macrofolliculare glandulae thyreoideae. Na kontrolnom pregledu u januaru 2024. godine pacijentkinja bez prethodno navedenih tegoba u vidu gušenja i osećaja pritiska u abdo-

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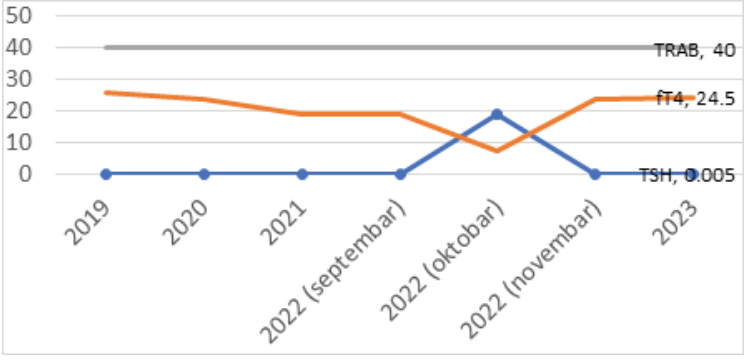
menu, TSH 7.21 fT4 16.4 na terapiji levotiroksin 175mcg. Pacijentkinja nastavila redukcionu dijetu u kućnim uslovima.

Ključne reči: hipertireoza, gojaznost, ovarijalni tumor

Prikaz slučaja: Pacijentkinja starosti 34 godine hospitalizovana je na Klinici za endokrinologiju radi započinjanja redukcije TM primenom dijetetskog režima i reevaluacije hipertireoze. Pacijentkinja kao glavne tegobe na prijemu navodi osećaj nedostatka vazduha i pritiska u abdomenu. Pacijentkinja je dobila u TM oko 70 kg od 2019. Godine, tokom koje joj je postavljena i dijagnoza Grejvs Bazedovljeve bolesti (TRAB>40). U septembru 2022. godine je operisana štitasta žlezda (izvađen desni režanj i istmus); PH nalaz: struma colloides cystica partim hyperplastica gl. thyreoideae. Pacijenktinja je na prijemu i dalje na tireosupresivnoj terapiji (tiamazol 10mg 1x1). Sve vreme od postavljanja dijagnoze Grejvsove bolesti, i pored tireosupresivne terapije, vrednosti fT4 su visoke. U ličnoj anamnezi navodi punkciju vodene ciste desnog jajnika i insulinsku rezistenciju, zbog čega je na terapiji metforminom. U objektivnom nalazu pacijentkinja je morbidno gojazna (ITM 62 kg/m^2). Prisutan egzoftalmus desnog oka. Na vratu izražen acantosis nigricans. Trbuh iznad ravni grudnog koša, mek, napet, palpatorno bolno neosetljiv. Na DE prisutan otok i hiperpigmentovane promene (Slika 1).

Slika 1. Fizikalni nalaz pacijentkinje na prijemu

Laboratorijske analize: U krvnoj slici leukopenija i normocitna anemija (Leu 3.4, Hgb 112, MCV 85). CRP blago povišen. Vrednost HbA1c je uredna (HbA1C 5%). Nema retencije azotnih materija. Elektrolitni status, proteinogram, hepatogram, lipidogram i urikemija su u granicama normale. Suprimovan TSH, uz visok fT4 (TSH <0.005, fT4 37.7), uz visoka TRAB (>40). Korigovana je doza tireosupresivne terapije i pacijentkinja je stavljena na redukcionu dijetu. **Radiografija srca i pluća**: uredan nalaz. **UZ štitaste žlezde**: hipoehogena, nehomogena struktura, reaktivni LN 6x11mm submandibularno. **UZ abdomena (inicijalni)**: slobodna tečnost u abdomenu, bez slobodne tečnosti u maloj karlici. Kod pacijentkinje je **ponovljen UZ abdomena**: gušća slobodna tečnost AP dijametra 21.9 cm. Na ginekološkom pregledu viđena anehogena formacija 110x80 mm iza i iznad uterusa, savetovan je pregled magnetnom rezonancom male karlice, koji nije urađen iz tehničkih razloga zbog konstitucije pacijentkinje. Gastroenterolog je ponovio UZ abdomena: viđen dilatiran **želudac** i potkožna kolekcija oko 240 mm. Urađena je gastroskopija, uzete su biopsije tankog creva, antruma i korpusa **želuca**, PH nalaz: 1. Superficijalni vilusni nivoi bez promena, 2. Lakostepena foveolarna hiperplazija, 3. *blaga inflamatorna promena mukoze korpusa sa fokalnim limfoidnim agregiranjem u bazalnom nivou. Urađen je perkutani punktat, u kome nisu dobijene maligne* ***ćelije***. Urađen je CT abdomena bez iv kontrasta: u projekciji desnih adneksa uočava se per magna cistična ekspanzivna tumorska promena dijametra 318x380x242 mm oštrih kontura, ispunjena seroznim tečnim sadržajem i okružena kapsulom (dif dg. cistadenom desnog jajnika). Pacijentkinja je predstavljena konzilijumu na Institutu za onkologiju i radiologiju Srbije (IORS), na kome je odlučeno da se u jednom aktu operativno ukloni tumor desnog jajnika i preostali levi režanj štitaste žlezde. Dana 21.09.2023. pacijentkinja je operisana na IORS-u, pri čemu je izvađen tumor težine oko 30 kg. PH nalaz: 1. cystadenoma mucinosum ovarii; 2. struma colloides micro et macrofolliculare glandulae thyreoideae. Na kontroli u januaru 2024. godine pacijentkinja bez prethodno navedenih tegoba u vidu gušenja i osećaja pritiska u abdomenu, TSH 7.21 fT4 16.4 (levotiroksin 175mcg). Oftalmopatija u regresiji. Korigovana doza levotiroksina. Pacijentkinja nastavila redukcionu dijetu u kućnim uslovima.



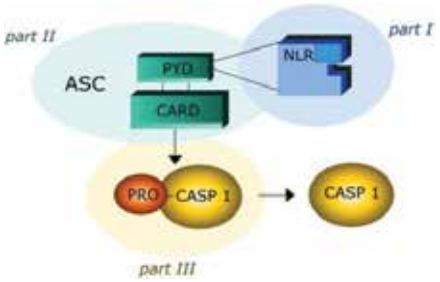
Grafik 1. Vrednost TSH, fT4 i TRAB od postavljanja dijagnoze Grejvs Bazedovljeve bolesti kod naše pacijentkinje

Diskusija: Hipertireoza je oboljenje kod koga postoji prekomerna koncentracija tiroidnih hormona u tkivima nastalim kao posledica povećane sinteze tiroidnih hormona, prekomernog oslobađanja prethodno formiranih tiroidnih hormona ili iz endogenih ili egzogenih ekstratiroidnih izvora. Prevalencija hipertireoze je 1,2–1,6%, od toga se klinička hipertireoza javlja u 0,5–0,6% i supklinčka hipertireoza u 0,7–1,0% slučajeva. Najčešći uzroci hipertireoze su Grejvsova bolest (GB), toksična multinodularna struma, toksični adenomi i nemi/bezbolni tiroiditis. Ređi uzroci hipertireoze su tiroiditis uzrokovan lekovima (tireotoksikoza indukovana amjodaronom tip 1 i tip 2), hyperemesis gravidarum, postpartalni tiroiditis, subakutni granulomatozni tiroiditis, dok u najređe uzroke spadaju TSH sekretujući adenom hipofize, struma ovarijuma i metastatski folikularni karcinom štitaste žlezde (1–6). Približno 3% žena i 0,5% muškaraca razvije GD tokom svog životnog veka (7). GB je organ-specifična autoimuna bolest čije glavne manifestacije su posledica cirkulacije autoantitela koja stimulišu hormonski receptor (TSH-R) koji dovodi do hipertireoze i strume. TSH-R-stimulišuća autoantitela su pretežno klase IgG1 i vezuju se za diskontinuirani epitop *leucine-rich* domena TSH-R, što pojačava proizvodnju intracelularnog cikličnog AMP i dovodi do oslobađanja tiroidnih hormona i rasta tireocita (8, 9). Oko 30% pacijenata sa GB ima članove porodice koji takođe imaju GB ili Hašimotov tiroiditis. Studije sa blizancima su pokazale da je 80% podložnosti za GB genetička i povezuje se sa haplotipovima HLA DR3 I HLA DR4, kao i lokusima gena za *cytotoxic T lymphocyte antigen-4, non-receptor protein tyrosine phosphatase 22* (PTPN22), *leucine zipper transcription factor 2* i CD40 (10). Klinička prezentacija hipertireoze kreće se od asimptomatske do tiroidne oluje. Povišeni nivoi tiroidnih hormona pojačavaju dejstvo kateholamina kroz povećan broj beta-adrenergičkih receptora na površini ćelije. Nastali adrenergični simptomi (palpitacije, netolerancija na toplotu, dijaforeza, tremor, dijareja) su najčešće manifestacije hipertireoze. Hipermetabolizam izaziva gubitak težine uprkos povećanom apetitu. Neuromuskularni simptomi uključuju slabost proksimalnih mišića. Psihijatrijski simptomi se kreću od anksioznosti do psihoza. Pacijenti sa dugotrajnim nelečenim hipertireoidizmom mogu razviti atrijalnu fibrilaciju (10% do 15% pacijenata) ili srčanu insuficijenciju (5,8%) (11, 12, 13). Znaci koji su patognomonični za Grejvsovu bolest uključuju orbitopatiju, pretibijalni miksedem (dermopatiju štitaste žlezde) i akropatiju štitaste žlezde, koji se javljaju kod 25%, 1,5% i 0,3% pacijenata. Grejvsova orbitopatija se manifestuje kao egzoftalmus ili periorbitalni edem, a može izazvati fotofobiju, prekomerno suzenje, povećanu osetljivost oka na vetar ili dim, ili osećaj stranog tela u očima. U teškim slučajevima može se razviti zamagljen vid, diplopije ili smanjena percepcija boja. Pušenje povećava rizik od razvoja Grejvsove orbitopatije (14). Pretibijalni miksedem razvija se aktivacijom fibroblasta i manifestuje se kao oticanje preko tibija sa kožom koja poprima izgled *peau d'orange* (narandžine kore) (15). Akropatija štitaste žlezde, koja je veoma retka, obuhvata nastanak batičastih prstiju na rukama i nogama sa

oticanjem mekih tkiva šaka i stopala (16). Merenje TSH u serumu ima najveću osetljivost i specifičnost od svih laboratorijskih testova koji se koriste u dijagnostikovanju hipertireoze i treba ga koristiti kao početni skrining test. Dijagnostička tačnost se poboljšava kada se u postavljanju dijagnoze zajedno mere TSH i fT4. Kada je hipofizno tiroidna osovina očuvana male promene u fT4 izazivaju velike promene u serumskoj koncentraciji TSH. Serumski TSH je senzitivniji od direktnog merenja tiroidnih hormona u proceni viška istih. U kliničkom hipertiroidizmu koncentracije hormona ft4 i T3 u serumu su povišene, uz suprimovan TSH, dok kod blažih formi serumska koncentracija T4 i fT4 može biti normalna, samo serumski fT3 povišen sa nedetektabilnim vrednostima TSH. TSH receptorska antitela su specifičan biomarker za GB (17). Ultrazvuk štitaste žlezde je neinvazivna, brza i precizna dijagnostička metoda koja se koristi u početnom dijagnostičkom pregledu i određivanju etiologije hipertireoze i istovremenom otkrivanju čvorova u štitastoj žlezdi. Štitasta žlezda kod pacijenata sa GB se obično ultrazvučno vidi kao difuzno uvećana i hipoehogena. Kod nelečene GB moguće je kolor doplerom utvrditi postojanje mnogobrojnih malih regiona sa povećanim intratiroidnim protokom nazvanih „tiroidni inferno". Kombinacija laboratorijskih analiza i UZ dijagnostike smanjuje potrebu za scintigrafijom u većini slučajeva. Tiroidna scintigrafija može biti korisna u proceni pacijenata pre tretmana radioaktivnim jodom, pogotovu kada je prisutna koegzistirajuća multinodularna struma (18). Izbor modaliteta lečenja hipertireoze zavisi od starosti pacijenta, simptoma, komorbiteta i prioriteta. GB zahteva jedno od tri opcije lečenja: tireosupresivnu terapiju (metimazol ili propiltiouracil), primenu radioaktivnog joda ili tiroidektomiju. Tireosupresivna terapija može biti dugotrajna terapija ili privremena do nekog drugog modaliteta lečenja. Kada se tireosupresivna terapija prekine, 30–70% pacijenata ima recidiv bolesti uglavnom unutar prve godine. Nakon prekida terapije funkciju štitaste žlezde je neophodno pratiti svakih jedan do tri meseca 6–12 meseci. Krvna slika i hepatogram treba da se urade pre početka uzimanja anitiroidnih lekova. Naknadno rutinsko praćenje krvne slike nije potrebno, osim u slučaju povišene telesne temperature i faringitisa. Četiri nedelje nakon započinjanja terapije neophodno je odrediti fT4 i T3, potom na 4–8 nedelja radi prilagođavanja doze. Kada se vrednosti fT4 i T3 normalizuju, prate se svaka 3 meseca. Tireosupresivnu terapiju treba nastaviti 12–18 meseci, a zatim je smanjiti ili prekinuti ako je TSH uredan. Ablacija štitaste žlezde radioaktivnim jodom je najčešći tretman Grejvsove bolesti u SAD. Kontraindikovan je u trudnoći, dok je umerena do teška Grejvsova orbitopatija relativna kontraindikacija, posebno kod pacijenata koji puše, jer radioaktivni jod može pogoršati oftalmopatiju. Većina pacijenata razvije trajni hipotiroidizam 2–6 meseci nakon ablacije i zahtevaju nadoknadu tiroidnim hormonima. Tireoidektomija je metoda izbora kod pacijenata sa kompresivnim simptomima i kod pacijenata sa kontraindikacijama za radioaktivni jod ili tireosupresivnu terapiju (19–21).

Gojaznost i hipertireoza

U gojaznosti postoji inflamacija niskog stepena. Molekularne studije su pokazale vezu između inflamacije niskog stepena, gojaznosti i aktivnosti intracelularnih kompleksa tipičnih za imune ćelije (inflamazomi) (Slika 2).



Slika 2. Struktura inflamazoma

Gojazni pacijenti imaju povećan rizik da razviju autoimune bolesti štitaste žlezde, dok su dijabetes melitus tip 2 i dislipidemija povezani sa agresivnijim oblicima Grejvsove oftalmopatije (22). Samo lečenje hipo ili hipertireoze može dovesti do povećanja telesne mase. Često postizanje eutiroidnosti kod pacijenata sa hipertireozom može dovesti do ponovnog, čak i prekomernog dobijanja u telesnoj masi. Mehanizam koji se nalazi u osnovi ovog fenomena još nije razjašnjen, ali se smatra da prelazak iz hiper u eutiroidno stanje može da podstakne nastanak gojaznosti kod predisponiranih pacijenata (22). Retrospektivna studija, koja je uključivala 133 pacijenta sa Grejvsovom bolešću koji su primili tireosupresivnu terapiju, operaciju ili terapiju radioaktivnim jodom, pokazala je da je lečenje hipotireoze posle tireoidektomije ili terapije radioaktivnim jodom povezano sa značajno većim povećanjem telesne težine u poređenju sa pacijentima koji su postigli eutireoidizam sa tireosupresivnom terapijom ili hemitiroidektomijom (23). Mehanizmi koji leže u osnovi direktnog efekta Grejvsove bolesti na povećanje telesne težine su još uvek nejasni. Jedna hipoteza je da smeđe masno tkivo (BAT) eksprimira TSH receptore koji se aktiviraju anti-TSH-R stimulirajućim antitelima Grejvsovih pacijenata. U stvari, TSH može stimulisati termogenezu vezivanjem za TSH receptor eksprimiran u adipocitima, što je funkcija uključena u održavanje toplotnog statusa tokom hipotireoze. Štaviše, in vivo akutna primena rekombinantnog humanog TSH u suprafiziološkim dozama izazvala je oslobađanje malih, ali značajnih količina leptina koje su bile proporcionalne masnom tkivu. Stoga je razumno pretpostaviti da TSH stimulirajuća aktivnost sama po sebi može imati važan efekat na adipogenezu, uglavnom na belo masno tkivo. S

druge strane, ovaj efekat može biti pojačan inflamatornim citokinima prisutnim kod Grejvsovih pacijenata (IL-1, IL-6 i TNFa) koji su u stanju da aktiviraju hipotalamus, hipofizu, osovinu nadbubrežne žlezde i lučenje kortizola (22). U metaanalizi sprovedenoj 2018. godine pokazano je da je gojaznost povezana sa hipotireozom, Hašimoto tiroiditisom, pozitivnim anti- TPO antitelima, ali ne i anti-TG antitelima i GB (24). U studiji sprovedenoj u Kini 2023. godine, u kojoj su posmatrani različiti fenotipovi gojaznosti i poremećaji štitaste žlezde, pokazano je da je prevalenca hipertireoze bila najviša u grupi metabolički nezdravih normalno uhranjenih ljudi, dok je prevalenca GB bila najviša kod metabolički zdravih gojaznih pacijenata. Metabolički nezdrave normalno uhranjene osobe imaju 1,6 puta veći rizik za kliničku hipertireozu i 1,8 puta viši rizik za GB u odnosu na metabolički zdrave normalno uhranjene osobe (25). Indeks telesne mase, insulin bazno i HOMA IR su u pozitivnoj korelaciji sa težinom kliničke slike Grejvsove oftalmopatije (26).

Tumori jajnika

Tumori jajnika predstavljaju čest entitet u praksi. Tumorske mase jajnika veličine 5–15 cm klasifikuju se kao veliki tumori, dok se oni dijametra preko 20 cm nazivaju ogromni tumori jajnika. Njihova učestalost je mala, jer se većina slučajeva dijagnostikuje rano tokom rutinskih ginekoloških pregleda ili se uoče kao uzgredan nalaz. Češće se javljaju u zemljama u razvoju, u kojima se zbog siromaštva i nedostupnosti medicinske pomoći pacijentkinje kasno javljaju na pregled. Vremenom se tegobe u vidu pritiska u abdomenu i otežanog disanja intenziviraju. Većina velikih tumora jajnika je benigna, prijavljeno je svega nekoliko malignih slučajeva velikih tumora jajnika. Poseban problem u kliničkoj praksi predstavljaju gojazne pacijentkinje kod kojih gojaznost prikriva velike intraabdominalne mase. Kod ovih pacijentkinja povećan je operativni rizik, zbog toga većina autora ističe značaj poboljšanja preoperativnog stanja, uključujući korekciju anemije, profilaksu tromboembolijskih događaja i poboljšanje kardijalnog statusa (27, 28, 29).

Zaključak

Prikazali smo slučaj gojazne pacijentkinje sa Grejvsovom hipertireozom, kod koje je tokom hospitalizacije otkrivena abdominalna tumorska masa porekla desnog jajnika. Nespecifične tegobe ove pacijentkinje su tokom godina praćenja pripisane gojaznosti i osnovnoj bolesti. Gojaznost je bolest koja može da maskira simptome mnogih drugih bolesti, dok je kod gojaznih pacijenata otežano i samo postavljanje dijganoze (ograničenje vizuelizacionih metoda) i lečenje (veći operativni rizik), zbog čega ovi pacijenti zahtevaju multidisciplinarni pristup.

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U prilogu dostavljen informisani pristanak pacijentkinje.
Ne postoje sukobi interesa.

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LARGE OVARIAN CYSTADENOMA MASKED BY OBESITY IN A PATIENT WITH GRAVES' HYPERTHYROIDISM

Abstract: Ovarian tumors are a common entity in clinical practice. Tumors with an ovarian mass diameter exceeding 20 cm are termed giant ovarian tumors. Their prevalence is low, as most cases are diagnosed early during routine gynecological examinations or are incidental findings. A 34-year-old patient was admitted to the Clinic for Endocrinology for the initiation of a weight loss regimen and reevaluation of hyperthyroidism. She reported gaining about 70 kg since 2019, during which she was also diagnosed with hyperthyroidism. In September 2022 she underwent thyroid surgery (right lobe and isthmus removed); histopathology result: colloid cystic goiter, partly hyperplastic thyroid gland. Upon admission, her main complaints were abdominal pressure and shortness of breath. On examination, the patient was morbidly obese (BMI 62 kg/m²). Initial and repeated abdominal ultrasound showed a well-defined subcutaneous fluid collection measuring about 240 mm, creating cellulitis in the anterior abdominal wall. A gynecological examination revealed an anechoic formation measuring 110x80 mm behind and above the uterus. A CT scan of the abdomen without IV contrast showed a large cystic expansive tumor change in the right adnexa measuring 318x380x242mm with sharp contours, filled with serous fluid, and surrounded by a capsule, differential diagnosis: cystadenoma of the right ovary. The patient was presented to the Oncology and Radiology Institute of Serbia (IORS) for a multidisciplinary consultation, where it was decided to remove the tumor of the right ovary and the remaining left lobe of the thyroid gland in one operation. On September 21, 2023, the patient was operated at IORS, where the tumor weighing about 30 kg was removed. Histopathology results: 1. mucinous cystadenoma of the ovary; 2. colloid goiter micro and macrofollicular thyroid gland. Follow-up in

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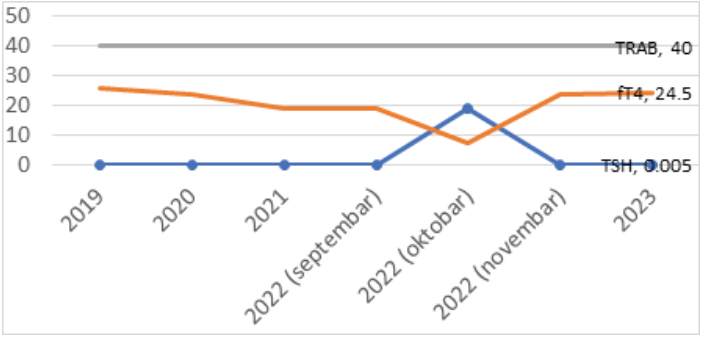
January 2024 showed the patient without previously mentioned symptoms of dyspnea and abdominal pressure, with TSH 7.21, fT4 16.4 on a dose of 175mcg levothyroxine. The patient continued with a reduction diet at home.

Keywords: hyperthyroidism, obesity, ovarian tumor

Case Presentation: A 34-year-old patient was admitted to the Clinic for Endocrinology for the initiation of a weight loss regimen and reevaluation of hyperthyroidism. The patient reported feeling short of breath and abdominal pressure upon admission. She had gained about 70 kg since 2019, during which she was diagnosed with Graves' disease (TRAB > 40). In September 2022, she underwent thyroid surgery (right lobe and isthmus removed); histopathology result: colloid cystic goiter, partly hyperplastic thyroid gland. The patient was still on antithyroid therapy (thiamazole 10 mg 1x1) at admission. Since the diagnosis of Graves' disease, despite antithyroid therapy, fT4 levels remained high. Her personal history includes a puncture of a right ovarian cyst and insulin resistance for which she was on metformin therapy. On examination, the patient was morbidly obese (BMI 62 kg/m²). Egzophthalmos of the right eye was present. The neck showed pronounced acanthosis nigricans. The abdomen was above the chest level, soft, tense, palpably tender but insensitive. On the lower extremities, there is swelling and hyperpigmented changes. (Figures 1).

Figure 1. Physical examination findings of the patient on admission

Laboratory Analyses: In the blood count, leukopenia and normocytic anemia (Leu 3.4, Hgb 112, MCV 85). CRP slightly elevated. HbA1C value was normal (HbA1C 5%). No retention of nitrogenous substances. Lipid and electrolyte status, total proteins and albumins, transaminases and uricemia were within normal limits. TSH was suppressed with high fT4 (TSH <0.005, fT4 37.7) and high TRAB (>40) (Graph1). The dose of antithyroid therapy was adjusted and the patient was placed on a reduction diet. Chest and lung radiography: normal findings; thyroid ultrasound: hypoechoic, heterogeneous structure, reactive lymph node 6x11 mm submandibularly. Initial abdominal ultrasound showed free fluid in the abdomen, with no free fluid in the pelvis. A follow-up abdominal ultrasound showed denser free fluid with an AP diameter of 21.9 cm. Gynecological examination revealed an anechoic formation 110x80 mm behind and above the uterus; a small pelvis MRI was advised but not performed due to the patient's constitution. Gastroenterology repeated abdominal ultrasound: dilated stomach and subcutaneous collection about 240 mm. A gastroscopy was performed, and biopsies were taken from the small intestine, antrum, and corpus of the stomach. The pathology report states: 1. superficial villous levels without changes 2. mild foveolar hyperplasia 3. mild inflammatory changes in the mucosa of the corpus with focal lymphoid aggregation at the basal level. A percutaneous puncture was also performed, which did not reveal malignant cells. CT abdomen without IV contrast revealed a large cystic expansive tumor change in the right adnexa measuring 318x380x242 mm with sharp contours, filled with serous fluid, and surrounded by a capsule, differential diagnosis: cystadenoma of the right ovary. The patient was presented to the Oncology and Radiology Institute of Serbia (IORS), where it was decided to remove the right ovarian tumor and the remaining left thyroid lobe in one operation. On September 21, 2023, the patient underwent surgery at IORS, where a tumor weighing about 30 kg was removed. Histopathology results: 1. mucinous cystadenoma of the ovary; 2. colloid goiter micro and macrofollicular thyroid gland. On follow-up in January 2024, the patient showed no previous symptoms of dyspnea and abdominal pressure, with TSH 7.21 fT4 16.4 (levothyroxine 175mcg). Ophthalmopathy was in regression. The dose of levotiroxine was adjustedand the patient continued a reduction diet at home.



Graph 1. Values of TSH, fT4, and TRAB from the time of diagnosis of Graves' disease in our patient

Discussion: Hyperthyroidism is a condition characterized by an excessive concentration of thyroid hormones in tissues, resulting from increased synthesis of thyroid hormones, excessive release of previously formed thyroid hormones, or endogenous or exogenous extrathyroidal sources. The prevalence of hyperthyroidism is 1.2-1.6%, with clinical hyperthyroidism at 0.5-0.6% and subclinical hyperthyroidism at 0.7-1.0%. The most common causes of hyperthyroidism are Graves' disease (GD), toxic multinodular goiter, toxic adenoma, and painless/subacute thyroiditis. Rarer causes include drug-induced thyroiditis (amiodarone-induced thyrotoxicosis types 1 and 2), hyperemesis gravidarum, postpartum thyroiditis, and subacute granulomatous thyroiditis, while the rarest causes include TSH-secreting pituitary adenoma, ovarian goiter, and metastatic follicular thyroid carcinoma (1-6). Approximately 3% of women and 0.5% of men will develop GD during their lifetime (7). GD is an organ-specific autoimmune disease, with its main manifestations resulting from the circulation of autoantibodies (Ab) that stimulate the hormone receptor (TSH-R), leading to hyperthyroidism and goiter. TSH-R-stimulating Ab are predominantly of the IgG1 isotype and bind to a discontinuous epitope in the leucine-rich domain of the extracellular TSH-R domain, which enhances intracellular cyclic AMP production, leading to the release of thyroid hormones and growth of thyrocytes (8,9). About 30% of GD patients have family members with GD or Hashimoto's thyroiditis. Twin studies have shown that 80% of the susceptibility to GD is genetic and is associated with HLA DR3 and HLA DR4 haplotypes, as well as loci for cytotoxic T lymphocyte antigen-4, non-receptor protein tyrosine phosphatase 22 (PTPN22), leucine zipper transcription factor 2 and CD40 (10). The clinical presentation of hyperthyroidism ranges from asymptomatic to thyroid storm. Elevated levels of thyroid hormones enhance the effects of catecholamines through an increased number of beta-adrenergic receptors on the cell surface. Resulting adrenergic symptoms (palpitations, heat intolerance, diaphoresis, tremor, diarrhea) are the most common manifestations of hyperthyroidism. Hypermetabolism leads to weight loss despite increased appetite. Neuromuscular symptoms include weakness of proximal muscles. Psychiatric symptoms range from anxiety to psychosis. Patients with long-term untreated hyperthyroidism may develop atrial fibrillation (10% to 15% of patients) or heart failure (5.8%) (11,12,13). Signs pathognomonic for Graves' disease include orbitopathy, pretibial myxedema (thyroid dermopathy), and thyroid acropachy, occurring in 25%, 1.5%, and 0.3% of patients, respectively. Graves' orbitopathy presents as exophthalmos or periorbital edema and may cause photophobia, excessive tearing, increased sensitivity to wind or smoke, or a foreign body sensation in the eyes. In severe cases blurred vision, diplopia or reduced color perception may develop. Smoking increases the risk of developing Graves' orbitopathy (14). Pretibial myxedema results from fibroblast activation and presents as swelling over the tibias with skin taking on an orange-peel appearance (15). Thyroid acropachy, which is very rare, includes the development of clubbing of

fingers and toes with swelling of soft tissues of the hands and feet (16). Measurement of serum TSH has the highest sensitivity and specificity among all laboratory tests used to evaluate suspected hyperthyroidism and should be used as the initial screening test. Diagnostic accuracy improves when both TSH and fT4 are measured together in the diagnosis. When the pituitary-thyroid axis is intact, small changes in fT4 cause large changes in serum TSH concentration. Serum TSH is more sensitive than direct measurement of thyroid hormones in assessing their excess. In clinical hyperthyroidism, serum concentrations of ft4 and T3 are elevated, with suppressed TSH, while in milder forms, serum concentrations of T4 and fT4 may be normal, with only serum fT3 elevated and undetectable TSH values. TSH receptor antibodies are a specific biomarker for GD (17). Thyroid ultrasound is a non-invasive, quick and accurate diagnostic method used in the initial diagnostic assessment and determining the etiology of hyperthyroidism while simultaneously detecting nodules in the thyroid gland. The thyroid gland in GD patients typically appears as diffusely enlarged and hypoechoic on ultrasound. In untreated GD color Doppler may reveal numerous small regions with increased intrathyroidal flow, termed "thyroid inferno." The combination of laboratory tests and ultrasound reduces the need for scintigraphy in most cases. Thyroid scintigraphy may be useful in assessing patients before radioactive iodine treatment, especially when coexisting multinodular goiter is present (18). The choice of treatment modality for hyperthyroidism depends on the patient's age, symptoms, comorbidities, and preferences. GD requires one of three treatment options: antithyroid drug therapy (methimazole or propylthiouracil), radioactive iodine therapy or thyroidectomy. Antithyroid drug therapy can be long-term or temporary until another treatment modality is chosen. When antithyroid therapy is stopped, 30-70% of patients experience disease recurrence, usually within the first year. After stopping therapy, thyroid function should be monitored every one to three months for 6-12 months. Blood counts and hepatograms should be done before starting antithyroid medications. Routine follow-up of blood counts is not necessary except in cases of elevated body temperature and pharyngitis. Four weeks after starting therapy, fT4 and T3 should be measured, followed by measurement every 4-8 weeks with dose adjustments. Once fT4 and T3 levels normalize, they are monitored every three months. Antithyroid therapy should be continued for 12-18 months, then reduced or discontinued if TSH is normal. Radioactive iodine ablation is the most common treatment for Graves' disease in the US. It is contraindicated during pregnancy, while moderate to severe Graves' orbitopathy is a relative contraindication, particularly in smokers, as radioactive iodine may worsen the eye disease. Most patients develop permanent hypothyroidism 2-6 months after ablation and require thyroid hormone replacement. Thyroidectomy is the treatment of choice for patients with compressive symptoms and for those with contraindications to radioactive iodine or antithyroid drug therapy (19-21).

Obesity and Hyperthyroidism: Obesity is strongly associated with low-grade inflammation. Molecular studies have demonstrated a link between low-grade inflammation in obesity and the activity of intracellular complexes typical of immune cells (inflammasomes) (Figure 2).

Figure 2. Structure of the inflammasome

Obese patients have an increased risk of developing autoimmune thyroid diseases, while type 2 diabetes mellitus and dyslipidemia are associated with more aggressive forms of Graves' ophthalmopathy (22). The relationship between obesity and autoimmune thyroid diseases can also go in the other direction, as treatment of hypo- or hyperthyroidism can lead to weight gain. Often, achieving euthyroidism in patients with hyperthyroidism can lead to renewed or even excessive weight gain. The mechanism underlying this phenomenon is not yet fully understood, but it is believed that transitioning from hyperthyroid to euthyroid state may promote obesity in predisposed individuals (22). A retrospective study involving 133 patients with Graves' disease who received anti-thyroid drugs (ATD), surgery or radioactive iodine (RAI) showed that treatment for hypothyroidism after thyroidectomy or post-RAI was associated with a significantly greater increase in body weight compared to patients who achieved euthyroidism with ATD or hemithyroidectomy (23). The mechanisms underlying the direct effect of Graves' disease on weight gain are still unclear. One hypothesis is that brown adipose tissue (BAT) expresses TSH receptors that are activated by anti-TSH-R stimulating antibodies in Graves' patients. In fact, TSH can stimulate thermogenesis by binding to TSH receptors expressed in adipocytes, a function involved in maintaining thermal status during hypothyroidism. Moreover, acute in vivo administration of recombinant human TSH in supra-physiological doses has triggered the release of small but significant amounts of leptin proportional to fat mass. Therefore, it is reasonable to assume that TSH-stimulating activity itself may have a significant effect on adipogenesis, mainly on white adipose tissue. On the other hand, this effect may be exacerbated by inflammatory cytokines present in Graves' patients (IL-1, IL-6, and TNFα) which can activate the hypothalamus, pituitary gland, adrenal axis and cortisol secretion (22). A meta-analysis conducted in 2018 showed that obesity is

associated with hypothyroidism, Hashimoto's thyroiditis, positive anti-TPO antibodies, but not anti-TG antibodies and GD (24). A study conducted in China in 2023, which examined different phenotypes of obesity and thyroid disorders, showed that the prevalence of clinical hyperthyroidism was highest in the metabolically unhealthy normal-weight group, while the prevalence of GD was highest in the metabolically healthy obese patients. Metabolically unhealthy normal-weight individuals have a 1.6 fold higher risk for clinical hyperthyroidism and a 1.8 fold higher risk for GD compared to metabolically healthy normal-weight individuals (25). Body mass index, fasting insulin, and HOMA IR are positively correlated with the severity of Graves' ophthalmopathy (26).

Ovarian Tumors: Ovarian tumors are a common entity in clinical practice. Ovarian masses ranging from 5 cm to 15 cm are classified as large tumors, while those over 20 cm in diameter are called giant ovarian tumors. Their incidence is low, as most cases are diagnosed early during routine gynecological examinations or are detected as incidental findings. They occur more frequently in developing countries, where poverty and lack of medical care result in patients presenting late. Over time, symptoms such as abdominal pressure and difficulty breathing intensify. Most large ovarian tumors are benign, with only a few cases of malignant large ovarian tumors reported. Obese patients pose a particular problem in clinical practice as obesity can obscure large intra-abdominal masses. In these patients, there is an increased operative risk, which is why most authors emphasize the importance of improving preoperative conditions, including correction of anemia, thromboembolism prophylaxisand enhancement of cardiac status (27, 28, 29).

Conclusion: We presented a case of an obese patient with Graves' hyperthyroidism in whom an abdominal tumor mass originating from the right ovary was discovered during hospitalization. The nonspecific symptoms of this patient were attributed to obesity and thyroid disease over years of follow-up. Obesity is a condition that can mask the symptoms of many other diseases, and diagnosing and treating obese patients can be challenging (due to limitations in visualization methods and increased operative risk) requiring a multidisciplinary approach.

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