Nataša Pevac[1], Biljana Olujić[2]

POJAVA GREJVSOVE ORBITOPATIJE NAKON OPERATIVNOG LEČENJA AUTOIMUNOG HIPERTIREOIDIZMA

Sažetak: Grejvsova orbitopatija (GO) je najčešća manifestacija autoimunog hipertireoidizma. Javlja se najčešće u prvoj godini posle postavljanja dijagnoze, a retko može da se javi i kod eutireoidnih i hipotireoidnih pacijenata. Nakon totalne tireoidektomije se može razviti kod oko 10–20% pacijenata, simptomi se obično javljaju nekoliko meseci do godinu dana od operacije. Rizik je veći kod pacijenata sa visokim titrom anti-TSH receptorskih antitela (TrAb), kod pušača i pacijenata koji nisu pravovremeno započeli supstitucionu terapiju levotiroksinom. Prva linija lečenja je primena intravenskih kortikosteroida. Bolesnica starosti 69 godina sa autoimunom tireoidnom bolešću se prezentovala autoimunim hipertireodizmom, započela lečenje tiresupresivnom terapijom, u trajanju od 5 godina, bez razvoja orbitopatije tokom lečenja. S obzirom na nepostizanje stabilizacije bolesti, sprovedena druga linija lečenja, urađena totalna tireoidektomija, sa posledičnim hipotireoidizmom i hipoparatireoidizmom. U daljem toku lečenja adekvatno supstituisana levotiroksinom, alfakalcidolom i kalcijumom. Operativno lečen adenokarcinom sigme, postoperativno primala hemioterapiju. Obolela 9 godina nakon operacije štitaste žlezde od COVID infekcije, nakon sprovedene redovne vakcinacije, lečena primenom biološke terapije, monoklonsko antitelo na "spike" protein SARS CoV 2 i antivirusnom terapijom. Nakon 11 godina od sprovedene totalne tireoidektomije dolazi do pojave srednje teške forme GO, umerenog stepena kliničke aktivnosti sa nestalnim dvoslikama, sa povišenim titrom TrAb. Primenom intravenske kortiroksteroidne terapije postiže se zadovoljavajući terapijski odgovor. Pojava GO, kao najčešće ekstratireoidne manifestacije autoimunog hipertireoidizma, izuzetno se retko javlja nakon više godina od početka lečenja hipertireoidizma, a još ređe nakon sprovođenja operativnog lečenja

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autoimunog hipertireoidizma. COVID infekcija i primena biološke terapije može biti okidač za pokretanje autoimunog procesa, kao i pridružene bolesti.

Ključne reči: Grejvsova orbitopatija, tireoidektomija, COVID infekcija

UVOD

Grejvsova orbitopatija (GO) je najčešća manifestacija autoimunog hipertireoidizma, najčešće se javlja u prvoj godini posle postavljanja dijagnoze, a retko može da se javi i kod eutireoidnih i hipotireoidnih pacijenata (1). Nakon totalne tireoidektomije se može razviti kod oko 10–20% pacijenata, simptomi se obično javljaju nekoliko meseci do godinu dana od operacije (2). Rizik je veći kod pacijenata sa visokim titrom anti-TSH receptorskih antitela, kod pušača i pacijenata koji nisu pravovremeno započeli supstitucionu terapiju levotiroksinom (3). Prva linija lečenja je primena intravenskih kortikosteroida (4).

PRIKAZ SLUČAJA

Bolesnica, 69 godina, javlja se na pregled endokrinologu zbog pojave Grejvsove orbitopatije (GO).

Dijagnoza autoimune hipertireoze je postavljena pre 12 godina (2006. godine), inicijalno lečena tireosupresivnom terapijom u trajanju od 5 godina, bez razvoja orbitopatije tokom lečenja. Nakon toga, s obzirom na to da nije došlo do stabilizacije bolesti, sprovedena druga linija lečenja, urađena totalna tireoidektomija (2011. godine), sa posledičnim hipotireoidizmom i hipoparatireoidizmom, postoperativno adekvatno supstituisani od samog početka supstitucionom terapijom levotiroksina, kalcidiola i kalcijuma, uz redovne kontrole. Marta 2023. godine javlja se na pregled endokrinologu zbog bola u desnom oku, crvenila i protruzije istog, bez pojačavanja bola pri pokretanju bulbusa. U jednom momentu primetila povremene dvoslike pri pogledu u stranu i zamućenje vida. Zaključeno da postoji srednje teška forma GO, CAS 3/7, sa nestalnim dvoslikama. Objektivnim pregledom, rime okuli asimetrične na račun retrakcije i protruzije desnog oka, obostrana retrakcija kapaka, više desnog oka, obostrano otoci kapaka i laka difuzna hiperemija konjunktiva, bez hemoze, plike i karunkuli bez promena. Učinjene laboratorijske analize su ukazale na povišen titar anti-TSH receptorskih antitela (TrAb) 6,9 IU/L, a magnetnom rezonancom orbita verifikovana obostrana proptoza nešto izraženije desno, izmenjeni i zadebljali orbitalni mišići donji pravi i medijalni pravi sa desne strane i uvećano retrobulbarno masno tkivo i proptoza izraženije na OD. Obavljen oftalmološki pregled.

U ličnoj anamnezi, prema medicinskoj dokumentaciji, 2020. godine operativno lečen adenokarcinom sigme sa privremenom stomom, nakon 2 godine urađena rekonstrukcija, postoperativno lečena hemioterapijom. 2021. godine vakcinisana protiv uzročnika SARS COV 2 infekcije, u dve doze BIBP COVID 19 (inaktivisanom cela virusna čestica). Kod pacijentkinje 2022. godine potvrđena infekcija SARS COV 2 virusom, lečena primenom biološke terapije, monoklonsko antitelo protiv "spike" protein (Casirivimab/ imdevimab), uz antivirusnu terapiju (favipiravir). Na osnovu rezultata funkcionalnog i morfološkog ispitivanja donešena odluka da se započne lečenje 12-nedeljnim kortikosteroidnim (KS) protokolom metilprednizolonom (MP).

Evaluacijom postterapijskog efekta nakon četiri meseca zaključeno da je došlo do poboljšanja bolesti u vidu smanjenja stepena kliničke aktivnosti GO, redukcije otoka kapaka obostrano, manjeg stepena protruzije, iščezavanja povremenih dvoslika, registrovan pad u titru TSH receptorskih antitela (TRAb 2,7 IU/L).

DISKUSIJA

Grejvsova bolest je autoimunska bolest štitaste žlezde, kod koje dolazi do stvaranja TSH receptorskih antitela (TrAb), koja se vezuju za TSH receptore tireocita i hronično ga aktiviraju, bez obzira na regulatorne mehanizme hipofize, čime dolazi do pojačane sekrecije trijodtironina (T3) i tiroksina (T4) (1). Paralelno, autoimunski proces zahvata i orbitalno tkivo (5). GO je najčešća manifestacija autoimunog hipertireoidizma, najčešće se javlja u prvoj godini posle dijagnoze, a retko može da se javi i kod eutireoidnih i hipotireoidnih pacijenata (6). Oko 80% slučajeva GO je povezano sa hipertireoidizmom, ali može da se javi pre, za vreme i nakon uspostavljanja eutiroidne funkcije na terapiji hipertireoidizma (7).

Ključna uloga u patogenezi je ekspresija TSH receptora i IGF 1 receptora na orbitalnim fibroblastima, koje aktiviraju TrAb, aktivacija receptora (TSHR/IGF-1) pokreće imunološku kaskadu (7). Fibroblasti proliferišu, diferencijacija u miofibroblaste, dovode do uvećanja mišićne mase i diferencijacije u adipocite, što dovodi do uvećanja retrobulbarnog masnog tkiva, povećana sekrecija glikozaminoglikana dovodi do zadržavanja vode i otoka tkiva (7). Rane inflamatorne promene podrazumevaju nakupljanje T limfocita, CD4+ i CD8+, dok su B limfociti retko prisutni, kao i makrofazi i mastociti (7). Najčešći simptomi Grejvsove orbitopatije su promene u izgledu usled retrakcije kapaka, sa ili bez proptoze, zatim osećaj peska u očima, suzenje i fotofobija, te diplopije u težim kliničkim slikama (4). Najčešći znaci orbitopatije su retrakcija gornjeg kapka, prisutna u 90–98% pacijenata sa bočnim proširenjem koje je patognomonično za GO. Ostali znaci uključuju crvenilo, otečenost konjunktive,

proptozu, egzoftalmus i lagoftalmus u težim slučajevima. Terapijski pristup zavisi od procene aktivnosti i težine bolesti (4).

Za procenu aktivnosti bolesti koristi se CAS (rezultat kliničke ativnosti), koji uključuje sedam parametara koji se boduju jednim bodom: retrobulbarni bol u miru, retrobulbarni bol pri pokretu bulbusa, crvenilo kapka, crvenilo konjunktiva, otok kapka, edem plika i karunkula i hemoza. Zbir bodova veći ili jednak 3 predstavlja aktivnu GO (Tabela 1) (4).

Tabela 1. Skor kliničke aktivnosti (*CAS – Clinical Activity Score*) za procenu aktivnosti orbitopatije

1.	Spontano prisutan bol retrobulbarno
2.	Bol pri pokretu očne jabučice
3.	Eritem kapka
4.	Hiperemija konjunktive
5.	Hemoza
6.	Edem karunkule
7.	Edem očnih kapaka

Za procenu težine oboljenja se koriste EUGOGO preporuke za klasifikaciju težine GO (Tabela 2)

1. GO koje ugrožavaju vid: Pacijenti koji imaju distiroidnu optičku neuropatiju i/ili oštećenje kornee. Zahteva hitno lečenje.
2. Srednje do teške GO: Pacijenti imaju jednu ili više od navedenih promena: retrakcija kapaka ≥ 2mm, srednja do teška zahvaćenost mekih tkiva, egzoftalmus ≥ 3mm, stalne ili nestalne diplopije. Lečenje se sprovodi imunosupresivima ili hirurški dekompresijom.
3. Blage GO: Pacijenti imaju jednu ili više od navedenih promena: retrakcija kapaka < 2mm, blaga zahvaćenost mekih tkiva, egzoftalmus < 3mm, povremene ili odsutne diplopije i iritacija kornee (osetljiva na lubrikante).

Tabela 2. Klasifikacija težine Graves-ove orbitopatije – EUGOGO

GO koje ugrožavaju vid	Pacijenti koji imaju distiroidnu optičku neuropatiju i/ili oštećenje kornee. Zahteva hitno lečenje.
Srednje do teške GO	Pacijenti imaju jednu ili više od navedenih promena: retrakcija kapaka ≥ 2mm, srednja do teška zahvaćenost mekih tkiva, egzoftalmus ≥ 3mm, stalne ili nestalne diplopije. Lečenje se sprovodi imunosupresivima ili hirurški dekompresijom.
Blage GO	Pacijenti imaju jednu ili više od navedenih promena: retrakcija kapaka < 2mm, blaga zahvaćenost mekih tkiva, egzoftalmus < 3mm, povremene ili odsutne diplopije i iritacija kornee (osetljiva na lubrikante).

Imidžing metode koje se koriste su ultrasonografija, magnetna rezonanca, oktreosken (scintigrafija) (8).

U terapiji GO prvi cilj je uspostaviti medikamentno eutireoidno stanje, te lečiti orbitopatiju po protokolu kortikosteroidima i/ili biološkom terapijom (7).

Prva linija lečenja aktivnih i srednje teških GO je primena intravenskih glukokortikoida, koji su efikasniji, bolje se tolerišu i imaju manje neželjenih efekata u odnosu na oralnu terapiju. Protokol podrazumeva primenu jednom nedeljno, tokom 12 nedelja, prvih 6 nedelja doza od 500 mg metilprednizolona, a potom 6 nedelja 250 mg metilprednizolona. Veće doze se mogu koristiti za teže oblike, ali kumulativna doza ne bi trebalo da prelazi 8 g po ciklusu (9).

Druga linija lečenja je primena biološke terapije (tocilizumab, rituksimab, teprotumumab) (10).

Nakon totalne tireoidektomije GO se može razviti kod oko 10–20% pacijenata, simptomi se obično javljaju nekoliko meseci do godinu dana od operacije. Rizik je veći kod pacijenata sa visokim titrom anti-TSH receptorskih antitela, kod pušača i pacijenata koji nisu pravovremeno započeli supstitucionu terapiju levotiroksinom. Radiojodna terapija (RAI) nosi veći rizik za razvoj GO. Grejvsova bolest (GB) je autoimuna bolest, a ne bolest same štitaste žlezde, te operativnim lečenjem autoimuni odgovor može da perzistira (7).

ZAKLJUČAK

U celini, prikazali smo bolesnicu kod koje se srednja teška forma Grejvsove orbitopatije javila 11 godina, što je izuzetno retko, nakon operativnog lečenja autoimunog hipertireoidizma, koja je prethodno lečena u trajanju od 5 godina tireosupresivnom terapijom, a u vreme aktivne bolesti nije došlo do razvoja GO, kao najčešće ekstratireoidne komplikacije autoimunog hipertireoidizma. Mogući razlog, okidač

ponovne aktivacije autoimunog procesa, može biti COVID infekcija i primena biološke terapije, kao i pridružene bolesti, budući da je GB sistemska autoimuna bolest, a ne samo bolest štitaste žlezde.

Primena prve linije lečenja, kortikosteroidna terapija, dovela je do zadovoljavajućeg terapijskog odgovora.

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DEVELOPMENT OF GRAVES' ORBITOPATHY FOLLOWING SURGICAL TREATMENT OF AUTOIMMUNE HYPERTHYROIDISM

Abstract: Graves' orbitopathy (GO), the most common extrathyroidal manifestation of autoimmune hyperthyroidism, typically occurs within the first year after diagnosis, although it may rarely develop in euthyroid and hypothyroid patients as well. Following total thyroidectomy, GO may develop in approximately 10–20% of patients, with symptoms usually appearing several months to one year after surgery. The risk is higher in patients with elevated titers of thyrotropin receptor antibodies (TRAb), smokers, and patients who do not initiate levothyroxine replacement therapy in a timely manner. Intravenous corticosteroid therapy represents the first-line treatment for active disease. A 69-year-old female patient with autoimmune thyroid disease initially presented with autoimmune hyperthyroidism and received antithyroid drug therapy for five years without developing orbitopathy during treatment. Due to failure to achieve sustained disease control, second-line treatment was implemented, and total thyroidectomy was performed, resulting in hypothyroidism and hypoparathyroidism. Subsequently, she was adequately substituted with levothyroxine, alfacalcidol, and calcium supplementation. The patient also underwent surgery for colon adenocarcinoma and received chemotherapy postoperatively. Nine years after thyroidectomy, despite regular vaccination, she developed COVID-19 infection and was treated with biologic therapy consisting of a monoclonal antibody targeting the SARS-CoV-2 spike protein, together with antiviral treatment. Eleven years after total thyroidectomy, the patient developed moderate-to-severe GO with moderate clinical activity, intermittent diplopia, and elevated TRAb levels. Treatment with intravenous corticosteroids resulted in a satisfactory therapeutic response. The occurrence of GO, as the most common extrathyroidal manifestation of autoimmune hyperthyroidism, is exceptionally rare several years after the onset of hyperthyroidism and even more uncommon following surgical treatment of autoimmune

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hyperthyroidism. COVID-19 infection, biologic therapy, and coexisting comorbidities may have acted as potential triggers for reactivation of autoimmune processes in this patient.

Keywords: Graves' orbitopathy, thyroidectomy, COVID-19 infection

INTRODUCTION:

Graves' orbitopathy (GO), the most common extrathyroidal manifestation of autoimmune hyperthyroidism, typically occurs within the first year after diagnosis, although it may rarely develop in euthyroid and hypothyroid patients (1). Following total thyroidectomy, GO may develop in approximately 10–20% of patients, with symptoms usually occurring several months to one year after surgery (2). The risk is higher in patients with elevated thyrotropin receptor antibody (TRAb) levels, smokers, and patients in whom levothyroxine replacement therapy was not initiated in a timely manner (3). Intravenous corticosteroid therapy represents the first-line treatment for active disease (4).

CASE REPORT:

A 69-year-old female patient was referred for endocrinological evaluation due to the development of Graves' orbitopathy (GO). The diagnosis of autoimmune hyperthyroidism had been established 12 years earlier (in 2006). Initially, the patient was treated with antithyroid drug therapy for five years without developing orbitopathy during treatment. Since stable disease control was not achieved, second-line treatment was subsequently implemented, and total thyroidectomy was performed in 2011, resulting in postoperative hypothyroidism and hypoparathyroidism. From the immediate postoperative period onward, the patient received adequate replacement therapy with levothyroxine, alfacalcidol, and calcium supplementation, with regular follow-up assessments. In March 2023, the patient presented for endocrinological evaluation due to pain in the right eye, associated with redness and proptosis, without worsening pain during eye movements. She also reported intermittent diplopia on lateral gaze and blurred vision. Moderate to severe GO with moderate clinical activity (CAS 3/7) and intermittent diplopia was diagnosed. Physical examination revealed asymmetric palpebral fissures due to retraction and proptosis of the right eye, bilateral eyelid retraction more pronounced in the right eye, bilateral eyelid edema, and mild diffuse conjunctival injection, without chemosis; the plica semilunaris and caruncle appeared normal. Laboratory analyses demonstrated elevated thyrotropin receptor antibody (TRAb) levels of 6.9 IU/L. Magnetic resonance imaging of the orbits showed bilateral

proptosis, more pronounced on the right side, enlargement and structural changes involving the right inferior rectus and medial rectus muscles, as well as increased retrobulbar adipose tissue with more prominent right-sided proptosis. Ophthalmologic evaluation was also performed. According to the patient's medical history and documentation, she underwent surgical treatment for sigmoid adenocarcinoma in 2020 with temporary stoma formation, followed by reconstructive surgery two years later, and subsequently received chemotherapy. In 2021, she received two doses of the BIBP COVID-19 vaccine (whole inactivated virus vaccine) against SARS-CoV-2 infection. In 2022, the patient developed a confirmed SARS-CoV-2 infection and was treated with biologic therapy consisting of monoclonal antibodies directed against the viral spike protein (casirivimab/imdevimab), together with antiviral therapy (favipiravir). Based on functional and morphological findings, treatment with a 12-week intravenous corticosteroid protocol using methylprednisolone (MP) was initiated. Post-treatment evaluation after four months demonstrated clinical improvement, including reduced GO clinical activity, bilateral reduction in eyelid edema, decreased degree of proptosis, complete resolution of intermittent diplopia, and a reduction in thyrotropin receptor antibody levels (TRAb 2.7 IU/L).

DISCUSSION:

Graves' disease (GD) is an autoimmune thyroid disorder characterized by the production of thyrotropin receptor antibodies (TRAb), which bind to thyrotropin receptors on thyrocytes and chronically stimulate them independently of pituitary regulatory mechanisms, resulting in increased secretion of triiodothyronine (T3) and thyroxine (T4) (1). Simultaneously, the autoimmune process also affects orbital tissues (5). Graves' orbitopathy (GO), the most common extrathyroidal manifestation of autoimmune hyperthyroidism, most frequently occurs within the first year following diagnosis, although it may rarely develop in euthyroid and hypothyroid patients (6). Approximately 80% of GO cases are associated with hyperthyroidism; however, GO may occur before, during, or after the establishment of euthyroidism during treatment of hyperthyroidism (7).

A key role in the pathogenesis of GO is attributed to the expression of thyrotropin receptors (TSHR) and insulin-like growth factor 1 receptors (IGF-1R) on orbital fibroblasts, which are activated by TRAb. Activation of the TSHR/IGF-1R pathway initiates an immune cascade (7). Orbital fibroblasts proliferate and differentiate into myofibroblasts, contributing to enlargement of extraocular muscles, while differentiation into adipocytes leads to expansion of retrobulbar adipose tissue. In addition, increased secretion of glycosaminoglycans promotes water retention and tissue edema (7). Early inflammatory changes include infiltration by T lymphocytes,

predominantly CD4+ and CD8+ cells, whereas B lymphocytes are less frequently present, together with macrophages and mast cells (7). The most common symptoms of GO include changes in appearance due to eyelid retraction, with or without proptosis, as well as a foreign-body sensation, excessive tearing, and photophobia, while diplopia is typically observed in more severe forms of the disease (4). The most common clinical sign of GO is upper eyelid retraction, observed in 90–98% of patients, often accompanied by lateral flare, which is considered highly characteristic of GO. Other manifestations include conjunctival redness and swelling, proptosis, exophthalmos, and lagophthalmos in more severe cases. The therapeutic approach depends on assessment of disease activity and severity (4).

Disease activity is assessed using the Clinical Activity Score (CAS), which includes seven parameters scored with one point each: spontaneous retrobulbar pain, pain on eye movement, eyelid redness, conjunctival redness, eyelid swelling, inflammation of the plica semilunaris and caruncle, and conjunctival edema (chemosis). A total score ≥3 indicates active GO (Table 1) (4).

Table 1. Clinical Activity Score (CAS) for evaluation of the activity of orbitopathy

1.	Spontaneous retrobulbar pain
2.	Pain on eye movements
3.	Eyelid erythema
4.	Conjunctival injection
5.	Chemosis
6.	Swelling of the caruncle
7.	Eyelid edema or fullness

Disease severity is assessed according to the European Group on Graves' Orbitopathy (EUGOGO) classification system (Table 2):

1. Sight-threatening GO: patients with dysthyroid optic neuropathy and/or corneal breakdown requiring urgent treatment.
2. Moderate to severe GO: patients presenting with one or more of the following findings: eyelid retraction ≥2 mm, moderate-to-severe soft tissue involvement, exophthalmos ≥3 mm, or constant/intermittent diplopia. Treatment consists of immunosuppressive therapy and/or surgical orbital decompression.

3. Mild GO: patients presenting with one or more of the following findings: eyelid retraction <2 mm, mild soft tissue involvement, exophthalmos <3 mm, intermittent or absent diplopia, and corneal irritation responsive to lubricants.

Table 2. Disease severity of the Graves' orbitopathy (GO) classification system- EUGOGO

Sight-threatening GO	Patients with dysthyroid optic neuropathy and/or corneal breakdown. Requires urgent treatment.
Moderate to severe GO	Patients presenting with one or more of the following findings: eyelid retraction ≥2 mm, moderate-to-severe soft tissue involvement, exophthalmos ≥3 mm, or constant/intermittent diplopia. Treatment consists of immunosuppressive therapy and/or surgical orbital decompression.
Mild GO	Patients presenting with one or more of the following findings: eyelid retraction <2 mm, mild soft tissue involvement, exophthalmos <3 mm, intermittent or absent diplopia, and corneal irritation (responsive to lubricants).

Imaging modalities used in the evaluation of GO include ultrasonography, magnetic resonance imaging (MRI), and octreotide scintigraphy (octreoscan) (8).

The primary therapeutic goal in GO is the establishment and maintenance of a euthyroid state, followed by treatment of orbitopathy according to disease activity and severity using corticosteroids and/or biologic therapy (7).

First-line treatment for active moderate-to-severe GO consists of intravenous glucocorticoids, which are more effective, better tolerated, and associated with fewer adverse effects than oral therapy. The recommended treatment protocol consists of weekly administration over 12 weeks, with methylprednisolone at a dose of 500 mg for the first six weeks followed by 250 mg for an additional six weeks. Higher doses may be used in more severe cases; however, the cumulative dose should not exceed 8 g per treatment cycle. (9)

Second-line treatment options include biologic therapies such as tocilizumab, rituximab, and teprotumumab (10). Following total thyroidectomy, GO may develop in approximately 10–20% of patients, with symptoms typically occurring several months to one year after surgery. The risk is increased in patients with elevated TRAb levels, smokers, and patients in whom levothyroxine replacement therapy was not initiated promptly. Radioiodine (RAI) therapy is associated with a greater risk of GO development. Graves' disease represents a systemic autoimmune disorder rather than a disease confined solely to the thyroid gland; therefore, autoimmune activity may persist despite surgical treatment. (7)

CONCLUSION

Overall, we presented a patient who developed moderate-to-severe Graves' orbitopathy 11 years after surgical treatment of autoimmune hyperthyroidism, an exceptionally rare occurrence. Prior to thyroidectomy, the patient had received antithyroid drug therapy for five years without developing GO during the active phase of hyperthyroidism, despite GO being the most common extrathyroidal manifestation of autoimmune hyperthyroidism. A possible trigger for reactivation of the autoimmune process may have been COVID-19 infection, treatment with biologic therapy, and the presence of associated comorbidities, considering that Graves' disease represents a systemic autoimmune disorder rather than a disease confined solely to the thyroid gland.

Administration of first-line treatment with intravenous corticosteroid therapy resulted in a satisfactory therapeutic response.

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