MIJASTENIJA GRAVIS I HRONIČNA INFLAMATORNA DEMIJELINIZACIONA POLINEUROPATIJA KOD PACIJENTA SA RECIDIVANTNIM TIMOMOM

PRIKAZ SLUČAJA

CASE REPORT

MYASTHENIA GRAVIS AND CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN A PATIENT WITH RECURRENT THYMOMA

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SAŽETAK

Mijastenija gravis (MG) i hronična inflamatorna demijelinizaciona polineuropatija (engl. *chronic inflammatory demyelinating polyneuropathy – CIDP*) su autoimunske bolesti usmerene na različite targete: kod mijastenije gravis, to je postsinaptička membrana skeletne muskulature, dok su kod *CIDP*-a u pitanju periferni nervi. Za razliku od mijastenije gravis, koju viđamo u značajnom procentu obolelih sa timomom, udruženost *CIDP*-a sa mijastenijom gravis i timomom je retkost.

Ovo je prikaz bolesnika sa dugogodišnjom anamnezom mijastenije gravis nesigurnog toka, koji je u više navrata operisan od recidiva timoma. Kod bolesnika se, posle dugogodišnje kliničke remisije od 16 godina, a u sklopu ponovne egzacerbacije timoma razvio *CIDP*, bez znakova mijastenične slabosti.

Ključne reči: mijastenija gravis, *CIDP*, timom

ABSTRACT

Myasthenia gravis (MG) and chronic inflammatory demyelinating polyneuropathy (CIDP) are autoimmune diseases aimed at different targets: in MG, it is the postsynaptic membrane of the skeletal musculature, while in CIDP, it is the peripheral nerves. Unlike MG, which can be observed in a significant percentage of patients with thymoma, the association of CIDP with MG and thymoma is rare.

This is a report on a patient with a long-term history of myasthenia gravis with an unstable course, who was operated on several times because of the recurrence of thymoma. In the patient, after a long-term clinical remission lasting 16 years, and as part of the re-exacerbation of the thymoma, CIDP developed without signs of myasthenic weakness.

Key words: myasthenia gravis, CIDP, thymoma

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UVOD

Pozitivan efekat timektomije kod obolelih od mijastenije gravis (MG) je poznat već duže od jednog veka. Pojava timoma je često udružena sa razvojem mijastenije gravis. Obično su to najteže forme MG-a, vrlo brzog toka i generalizovanog karaktera. Kada se u osnovi mijastenije dijagnostikuje timom, timektomija je obavezna.

Nestabilna klinička slika u postoperativnom toku je razlog da se posumnja na rest timusnog tkiva ili recidiv timoma, kada je indikovana kontrolna radiografska eksploracija grudnog koša. U slučaju da se kontrolnom radiografijom potvrdi ponovno javljanje timoma, pristupa se njegovom ponovnom operativnom uklanjanju.

Pojava timoma ređe može biti udružena i sa nekim drugim autoimunskim oboljenjima, kao i sa polineuropatijama. Hronična inflamatorna demijelinizaciona polineuropatija (engl. *chronic inflammatory demyelinating polyneuropathy – CIDP*), kao vrsta polineuropatije koja prati timom, jeste retkost.

Iako se radi o organ-specifičnim autoimunskim bolestima, *CIDP* i MG imaju različite targete autoimunskog odgovora i retko se viđaju zajedno. Stoga je cilj jasan – prezentovati ovako raritetan događaj.

PRIKAZ BOLESNIKA

Pacijent star 44 godine je, sredinom 2005. godine, u vremenu od svega par dana, razvio dominantno proksimalnu slabost ekstremiteta, praćenu epizodom otežanog gutanja, kada mu je klinički, neurofiziološki i imunološki postavljena dijagnoza seropozitivne mijastenije gravis (*MGFA* IV) [1].

Po uvođenju antiholinesterazne i imunosupresivne terapije, pacijent je uveden u kliničku remisiju. Neposredno po kliničkoj stabilizaciji mijastenične slabosti, pacijent je i timektomisan, a pato-histološki nalaz timusa je potvrdio raniju sumnju da se radi o timomu. Timektomija je obavljena uobičajenim klasičnim, transsternalnim pristupom i bila je praćena intrahospitalnim komplikacijama, u smislu povećane postoperativne drenaže iz operisane regije, što na kraju ipak nije zahtevalo hiruršku reintervenciju.

U postoperativnom toku, brzo je postignuta potpuna klinička remisija, da bi posle dve godine praćenja, zbog nestabilnog kliničkog toka, pacijentu bio ponovljen *MSCT* grudnog koša, na kojem je viđen rest timomskog tkiva, zbog čega pacijent biva re-timektomisan 2007. godine. Nakon toga, sprovedeno je četiri ciklusa hemioterapije, a zatim i 20 zračenja, tako da je, posle godinu dana hematološkog praćenja i lečenja, bilo završeno i lečenje maligne bolesti. Na redovnim neurološkim kontrolama, postepeno je redukovana te-

INTRODUCTION

The positive effect of thymectomy in patients with myasthenia gravis (MG) has been known for more than a century. The occurrence of thymoma is often associated with the development of myasthenia gravis. These are usually the most severe forms of MG, with a very rapid course and a generalized character. When thymoma is diagnosed as the underlying condition of myasthenia gravis, thymectomy is mandatory.

An unstable clinical presentation in the postoperative course is a reason to suspect that there are remains of thymic tissue or that there is a recurrence of thymoma, in which case a follow-up radiographic exploration of the chest is indicated. In the event that thymoma recurrence is confirmed with follow-up radiography, its surgical removal is performed again.

The occurrence of thymoma can rarely be associated with other autoimmune diseases, as well as with polyneuropathies. Chronic inflammatory demyelinating polyneuropathy (CIDP), as a type of polyneuropathy accompanying thymoma, is rare.

Although they are organ-specific autoimmune diseases, CIDP and MG have different targets of autoimmune response and are rarely seen together. Therefore, the goal is clear - to present such a rare event.

CASE REPORT

In mid-2005, over a period of only a few days, a 44-year-old patient developed predominantly proximal weakness of the extremities, accompanied by an episode of difficulty swallowing, upon which he was clinically, neurophysiologically, and immunologically diagnosed with seropositive myasthenia gravis (MGFA IV) [1].

After the introduction of anticholinesterase and immunosuppressive therapy, the patient achieved clinical remission. Immediately after the clinical stabilization of myasthenic weakness, thymectomy was performed in the patient, and the pathohistological findings of the thymus confirmed the earlier suspicion of thymoma. Thymectomy was performed using the standard transsternal approach and was accompanied by intrahospital complications, in terms of increased postoperative drainage from the operated region, which ultimately did not require surgical reintervention.

In the postoperative course, a complete clinical remission was quickly achieved, and after two years of follow-up, due to an unstable clinical course, the patient underwent a repeated MSCT of the chest, which revealed remnant thymoma tissue, which is why the patient underwent a re-thymectomy in 2007. After that, four cycles of chemotherapy were administered, followed by 20 radiations, so that, after a year of hematological monitoring and therapy, the treatment of the

rapija, tako da je postignuta potpuna klinička remisija od 2012. godine.

Pacijent se ponovo javio neurologu avgusta 2021. godine, šest meseci posle preležane KOVID-19 infekcije blažeg stepena, koja nije zahtevala hospitalizaciju. Ovoga puta se žalio na parestezije tipa žarenja, trnjenja i „mravinjanja" u stopalima, a kasnije i u šakama, koja se razvila tokom prethodnih tri do četiri meseca, a za taj period je pacijent naveo gubitak od 5 – 6 kg telesne težine, što je bilo praćeno pojavom herpes zostera torakalne regije. Negirao je ovom prilikom mišićnu slabost i zamorljivost.

Neurofiziološki nalaz je ukazivao na demijelinizacionu senzomotornu stečenu poliradikuloneuropatiju umerenog stepena, što je uz nalaz albuminocitološke disocijacije u likvoru (1,4 g/l proteinorahija) ukazivalo na *CIDP*. Kontrolni *MSCT* grudnog koša je otkrio manju mekotkivnu formaciju, u nivou od 8. do 10. rebra, čiji je PH nalaz posle punkcione biopsije ove promene upućivao na recidiv timoma B2 gradusa. Pacijent je lečen lekovima za neuropatski bol, a rest timoma je uklonjen video-asistiranom torakoskopskom hirurgijom (engl. *video-assisted thoracoscopic surgery – VATS*), tako da je posle višemesečnog lečenja pacijent ponovo bio u kliničkoj remisiji.

DISKUSIJA

Kako je timus odgovoran za započinjanje imunoloških procesa kod obolelih od mijastenije gravis, uklanjanje timusa timektomijom, pored konzervativne terapije, igra važnu ulogu u lečenju obolelih od mijastenije gravis [1]. Timektomijom se obezbeđuje stabilniji klinički tok bolesti, brža klinička remisija i značajna redukcija potrebne konzervativne terapije [2].

Kada je u osnovi mijastenije gravis dijagnostikovani timom, timektomija je obavezna. Prikazani pacijent je na taj način i lečen – nedugo po postavljanju dijagnoze, učinjena je timektomija transsternalnim pristupom.

Sternotomija, kao optimalni metod hirurškog lečenja, jeste klasičan način na koji se timektomija obavljala dugi niz godina. Po prvi put je timektomiju na ovaj način, u lečenju MG-a, obavio Alfred Blelok, 1939. godine. Sternotomijom je bio obezbeđen otvoreni i široki pristup torakalnoj šupljini, kao i bolji uvid u operativno polje, mada je ovo podrazumevalo radikalno otvaranje grudnog koša.

Timektomija je putem sternotomije uspešno obavljana dugi niz godina u našoj ustanovi, na Vojnomedicinskoj akademiji u Beogradu [3]. Na ovaj način je prikazani pacijent prvi put operisan 2005. godine (Slika 1), a zatim zbog ponovne pojave timoma i reoperisan, dve godine kasnije, kada je sprovedeno i hematološko lečenje, iza čega je usledila potpuna višegodišnja klinička remisija.

malignant disease was completed. At regular neurological check-ups, the therapy was gradually reduced, so that a complete clinical remission was achieved in 2012.

The patient visited the neurologist again in August 2021, six months after having a mild COVID-19 infection that did not require hospitalization. This time he complained of paresthesia which manifested as burning, tingling, and prickling in his feet, and later in his hands, which had developed during the preceding three to four months, during which period the patient reported having lost 5 – 6 kg of body weight, which was accompanied by a break-out of herpes zoster in the thoracic region. He denied muscle weakness and muscle fatigue on this occasion.

The neurophysiological finding indicated moderate demyelinating sensorimotor acquired polyradiculoneuropathy, which together with the finding of albuminocytological dissociation in the cerebrospinal fluid (1.4 g/l proteinorrhagia) indicated CIDP. A follow-up MSCT of the chest revealed a smaller soft tissue formation, at the level between the 8th and the 10th rib, whose PH finding after puncture biopsy indicated the recurrence of B2 type thymoma. The patient was treated with drugs for neuropathic pain, and the remnant thymoma was removed using video assisted thoracoscopic surgery (VATS), so that after several months of treatment, the patient was again in clinical remission.

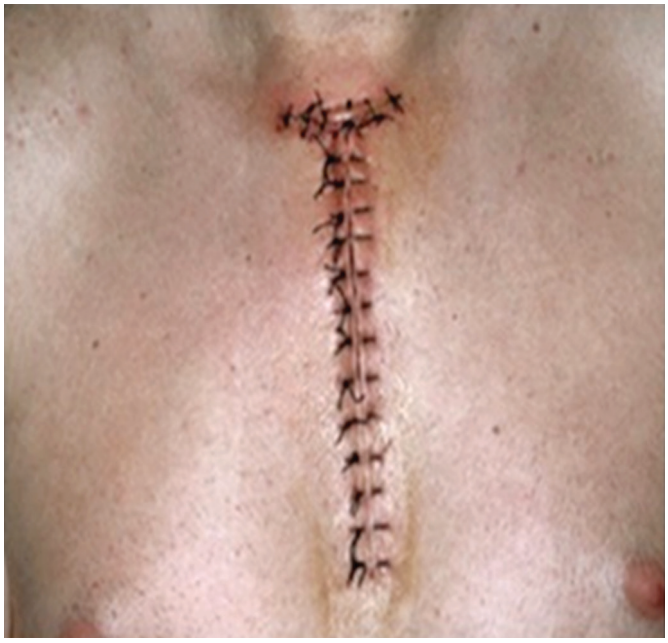
DISCUSSION

As the thymus is responsible for initiating immune processes in patients with myasthenia gravis, removal of the thymus by thymectomy, in addition to conservative therapy, plays an important role in the treatment of patients with myasthenia gravis [1]. Thymectomy ensures a more stable clinical course of the disease, faster clinical remission and a significant reduction of required conservative therapy [2].

When thymoma is diagnosed as the underlying condition of myasthenia gravis, thymectomy is mandatory. The patient whose case is presented here was indeed treated in this way - not long after the diagnosis, thymectomy was performed through the transsternal approach.

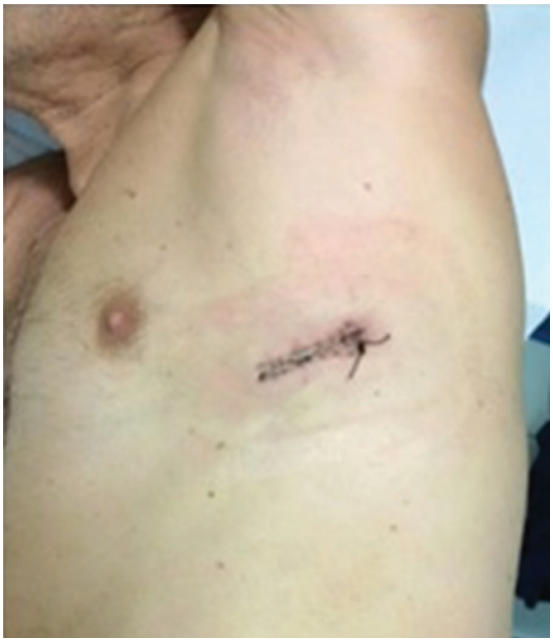
Sternotomy, as the optimal method of surgical treatment, was the standard mode of performing thymectomy for many years. Thymectomy was performed in this way for the first time, in the treatment of MG, by Alfred Blalock, in 1939. Sternotomy provided an open and wide access to the thoracic cavity, as well as a better insight into the operative field, although this implied a radical opening of the chest.

Thymectomy through sternotomy was successfully performed for many years in our institution, at the Military Medical Academy in Belgrade [3]. In this way, the



Slika 1. Timektomija transsternalnim putem

Figure 1. Thymectomy via the transsternal approach



Slika 2. Timektomija laparoskopskim putem pomoću video-asistirane torakoskopske hirurgije (*VATS*)

Figure 2. Thymectomy via the laparoscopic approach with video assisted thoracoscopic surgery (VATS)

nička remisija, od 2012. godine, tokom koje je pacijent bio i radno aktivan.

Dejvid Šugarbejker je, 1993. godine, prvi izveo video-asistiranu torakoskopsku hirurgiju (*VATS*), laparoskopskim pristupom timusu iz aksilarne jame, koja je manje invazivna i udružena sa manjim postoperativnim ožiljkom [3]. Na našim prostorima, *VATS* je po prvi put u hirurgiji timusa učinjena 2012. godine, i iza toga je postala isključivi način na koji se timektomija obavlja u lečenju mijastenije gravis u našoj ustanovi. Ovakvim pristupom se obezbeđuje kraća hospitalizacija, manje kliničkih komplikacija i bolji estetski postoperativni efekat [3,5]. Kako je poslednji recidiv timoma kod prikazanog pacijenta zabeležen u eri *VATS* timektomije, pacijent je poslednji put na taj način i operisan i lečen (Slika 2).

Tokom razvoja imunskog sistema, tolerancija na sopstvene antigene se razvija u koštanoj srži ili timusu. Abnormalnosti u timusu, bilo benigne bilo maligne, mogu biti udružene sa različitim autoimunskim i neuromišićnim bolestima. Među autoimunskim bolestima povezanim sa timomom, pominju se vitiligo, tireoiditis, autoimunski hepatitis, alopecija, aplazija eritrocita, autoimunska endokrinopatija [2].

Timomi se viđaju kod 10% do 15% obolelih od mijastenije gravis [6] i vezani su za najteže forme MG-a, obično akutnog ili subakutnog toka. Takva klinička prezentaciju je na početku bolesti zabeležena kod prikazanog bolesnika.

patient whose case is presented here was operated on for the first time in 2005 (Figure 1). Then, due to the recurrence of thymoma, he was reoperated on, two years later, when hematological treatment was also carried out, which was followed by complete clinical remission lasting a number of years, as of 2012, during which time the patient was able to work.

In 1993, David Sugarbaker was the first to perform video assisted thoracoscopic surgery (VATS), via the laparoscopic approach to the thymus from the axillary fossa, which is less invasive and associated with a smaller postoperative scar [3]. In our region, VATS was performed for the first time in thymic surgery in 2012, after which this has become the exclusive way in which thymectomy is performed in the treatment of myasthenia gravis in our hospital. This approach ensures a shorter hospital stay, fewer clinical complications and a better esthetic postoperative outcome [3,5]. As the latest recurrence of thymoma in the patient presented here was recorded in the era of VATS thymectomy, the patient's latest surgery and treatment was performed using this method (Figure 2).

During immune system development, tolerance to the body's own antigens develops in the bone marrow or thymus. Abnormalities in the thymus, whether benign or malignant, can be associated with various autoimmune and neuromuscular diseases. Among the autoimmune diseases associated with thymoma, vitiligo, thyroiditis, autoimmune hepatitis, alopecia, eryth-

Međutim, timomi ne moraju obavezno biti praćeni mijastenijom gravis. Prema nekim izveštajima, kod svega 40% timoma se razviju simptomi mijastenije [7].

U vrlo malom procentu, timomi mogu da budu praćeni i polineuropatijama – opisani su slučajevi kranijalne i periferne senzorne neuropatije, kao i neuromiotonija (Isakov sindrom) [8,9].

Udruženost timoma sa *CIDP*-om je retkost. O tome svedoči studija kojom je praćeno 29 pacijenata sa timomom, kada je 45% bolesnika pokazivalo znake autoimunosti, a među njima je samo jedan pacijent razvio *CIDP* [10]. Jos veća studija sa timomima, među 668 pacijenata je uočila autoimunska dešavanja kod 32% pacijenata [11].

Raritetni su opisi pacijenata kod kojih se pored višegodišnjeg trajanja mijasteničnih simptoma razvio i *CIDP* u sklopu dijagnostikovanog timoma [10], kao kod našeg pacijenta.

ZAKLJUČAK

Pojava timoma nije isključivo povezana sa razvojem mijastenije gravis. Viđaju se i druge autoimunske i paraneoplastične bolesti, udruženo sa timomom.

Preporuke su da se kod polineuropatija rezistentnih na farmakološko lečenje, učini radiološka eksploracija timusa, upravo zbog retkih slučajeva timoma koji mogu pratiti ovu bolest.

Sukob interesa: Nije prijavljen.

rocyte aplasia, and autoimmune endocrinopathy have been noted [2].

Thymomas are seen in 10% to 15% of patients with myasthenia gravis [6] and are associated with the most severe forms of MG, usually with an acute or subacute course. Such a clinical presentation was recorded at the beginning of the disease in the case presented here.

However, thymomas are not necessarily accompanied by myasthenia gravis. According to some reports, only 40% of thymomas develop symptoms of myasthenia gravis [7].

In a very small percentage of cases, thymomas can also be accompanied by polyneuropathies – cases of cranial and peripheral sensory neuropathy, as well as cases of neuromyotonia (Isaac's syndrome) have been described [8,9].

Association of thymoma with CIDP is rare. Evidence to this effect can be found in a study analyzing 29 patients with thymoma, where 45% of patients showed signs of autoimmunity, and among them only one patient developed CIDP [10]. An even larger study with thymomas, involving 668 patients, observed autoimmune events in 32% of patients [11].

There are rare descriptions of patients in whom, in addition to experiencing myasthenic symptoms for years, CIDP also developed as part of the diagnosed thymoma [10], as was the case with our patient.

CONCLUSION

The occurrence of thymoma is not exclusively related to the development of myasthenia gravis. Other autoimmune and paraneoplastic diseases are also observed to occur in association with thymoma.

It is recommended that, in case of polyneuropathies resistant to pharmacological treatment, radiological exploration of the thymus should be done, precisely because of the rare cases of thymoma that can accompany this disease.

Conflict of interest: None declared.

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