BOLEST TALOŽENJA LAKIH LANACA

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LIGHT CHAIN DEPOSITION DISEASE

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SAŽETAK

Bolest taloženja lakih lanaca predstavlja jedan od oblika bolesti taloženja monoklonskih imunoglobulina. Po učestalosti, reč je o retkom entitetu, koji se javlja kod osoba srednjeg životnog doba, češće muškog pola. Najčešće zahvata bubrege, sa kliničkom slikom nefritičkog sindroma, ali može biti lokalizovana i u drugim organima, kao što su jetra, pluća, srce, gastrointestinalni trakt, koža i drugi. U kliničkoj slici dominiraju simptomi i znaci zahvaćenog organa. Dijagnoza se najčešće postavlja biopsijom zahvaćenog organa, pri čemu se bojenjem na Kongo crveno razlikuje od amiloidoze lakih lanaca, a potom se vrši evaluacija koštane srži radi isključivanja drugih plazmocitnih diskrazija. Terapija je bazirana na terapijskim modalitetima za lečenje multiplog mijeloma, uključujući inhibitore proteazoma (bortezomib), uz autologu transplantaciju matičnih ćelija hematopoeze, ali i transplantaciju zahvaćenih organa ukoliko je došlo do potpunog gubitka funkcije. Podaci o terapiji monoklonskim antitelima (daratumumab) otvaraju nove terapijske mogućnosti u lečenju ove bolesti. Dijagnostika i lečenje ove bolesti zahtevaju multidisciplinarni pristup, prvenstveno nefrologa,hematologa i patologa.

Ključne reči: bolest deponovanja lakih lanaca, dijagnostika, terapija

ABSTRACT

Light chain deposition disease is one form of monoclonal immunoglobulin deposition disease. In terms of frequency, it is a rare entity that occurs in middle-aged people, more often males. It most often affects the kidneys, with a clinical picture of nephritic syndrome, but it can also be localized in other organs, such as the liver, lungs, heart, gastrointestinal tract, skin, and others. The symptoms and signs of the affected organ dominate the clinical picture. The diagnosis is most often established by biopsy of the affected organ, whereby Congo red staining differentiates it from light chain amyloidosis, and then bone marrow evaluation is performed to rule out other plasmacytic dyscrasias. Therapy is based on therapeutic modalities for treating multiple myeloma, including proteasome inhibitors (bortezomib), autologous hematopoietic stem cell transplantation, and transplantation of the affected organs if there has been a complete loss of function. Data on monoclonal antibody therapy (daratumumab) opens up new therapeutic possibilities for the treatment of this disease. Diagnosis and treatment of this disease require a multidisciplinary approach, primarily by nephrologists, hematologists, and pathologists.

Keywords: light chain deposition disease, diagnosis, therapy

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UVOD

Bolest taloženja lakih lanaca prema 5. reviziji klasifikacije bolesti hematopoetskih i limfoidnih tkiva Svetske zdravstvene organizacije pripada, kao najčešći entitet, grupi bolesti taloženja monoklonskih imunoglobulina, gde osim nje spadaju i bolesti taloženja teških lanaca, kao i bolesti taloženja lakih i teških lanaca [1]. Karakteriše je depozicija lakih lanaca imunoglobulina u različitim organima. Istaloženi laki lanci nemaju karakteristike amiloidne supstance, što ovu bolest razlikuje od amiloidoze lakih lanaca [2].

Bolest je prvi put dokazana 1976. godine na biopsijama bubrega dva pacijenta u Sjedinjenim Američkim Državama. Oba pacijenta su imala bubrežnu slabost, a veoma brzo su se razvile i druge manifestacije, najpre slabost jetre i neurološka simptomatologija, a zatim i srčano popuštanje, gastrointestinalne i endokrine manifestacije [3].

S obzirom na doskora limitirane mogućnosti za preciznu detekciju lakih lanaca učestalost ove bolesti je nepoznata. Češće se javlja kod muškaraca, a medijana starosti pri dijagnozi je 58 godina, dok je čak 36% pacijenata mlađe od 50 godina [4].

ETIOLOGIJA I PATOGENEZA

Etiologija ove bolesti je nepoznata.

U osnovi bolesti, mali patološki klon plazmocita niskog proliferativnog potencijala kao patološki protein proizvodi lake lance, dominantno kappa tipa [5]. Slobodni monoklonski laki lanci talože se u različitim organima kao neorganizovani, amorfni agregati, bez stvaranja depozita u vidu fibrilnih niti, što je i glavna razlika na mikroskopskom nivou između amiloidoze lakih lanaca i bolesti taloženja lakih lanaca [6]. Bolest taloženja lakih lanaca najčešće se manifestuje na bubrezima (kod oko 85% pacijenata), ređe u jetri, srcu, plućima, a vrlo retko u drugim organima [4].

Patofiziološki mehanizam oštećenja funkcije najbolje je izučen kod bubrežnih manifestacija, gde amorfni agregati lakih lanaca započinju kaskadu događaja koji vode ka mezangijalnoj ekspanziji i uvećanju ekstracelularnog matriksa neuobičajenog sastava (bogatog tenascinom), formirajući mezangijalne čvoriće koji zamenjuju normalni matriks bogat kolagenom IV [5,6]. Kao ređa, ali ponekad i prva manifestacija bolesti deponovanja lakih lanaca, u literaturi se pominje i tubulointersticijumska bolest bubrega. Najčešće se depoziti lakih lanaca viđaju duž tubularne bazalne membrane, uz linearne glomerularne i vaskularne depozite [7]. Retko, agregati lakih lanaca i Tamm Horsfalovog proteina mogu dovesti do zapušenja distalnih tubula i akutne bubrežne insuficijencije [8,9]. Iako promene na bubrežnim strukturama

INTRODUCTION

Light chain deposition disease, according to the 5th revision of the classification of hematopoietic and lymphoid tissue diseases of the World Health Organization, belongs, as the most common entity, to the group of monoclonal immunoglobulin deposition diseases, which also includes heavy chain deposition diseases, as well as light and heavy chain deposition diseases [1]. The deposition of immunoglobulin light chains in various organs characterizes it. Precipitated light chains do not have the characteristics of an amyloid substance, distinguishing this disease from light chain amyloidosis [2].

The disease was first proven in 1976 in the kidney biopsies of two patients in the United States of America. Both patients had kidney failure, and other manifestations developed very quickly, first liver weakness and neurological symptoms, and then heart failure and gastrointestinal and endocrine manifestations [3].

Given the recently limited possibilities for precise detection of light chains, the frequency of this disease is unknown. It occurs more often in men, and the median age at diagnosis is 58, while as many as 36% of patients are younger than 50 [4].

ETIOLOGY AND PATHOGENESIS

The etiology of this disease is unknown.

At the basis of the disease, a small pathological clone of plasma cells with a low proliferative potential produces light chains, predominantly of the kappa type, as a pathological protein [5]. Free monoclonal light chains are deposited in various organs as disorganized, amorphous aggregates without forming deposits in the form of fibrillar strands, which is the main difference at the microscopic level between light chain amyloidosis and light chain deposition disease [6]. The disease of deposition of light chains is most often manifested in the kidneys (in about 85% of patients), less often in the liver, heart, and lungs, and very rarely in other organs [4].

The pathophysiological mechanism of impaired function is best studied in renal manifestations, where amorphous aggregates of light chains initiate a cascade of events leading to mesangial expansion and enlargement of an extracellular matrix of unusual composition (rich in tenascin), forming mesangial nodules that replace the standard matrix rich in collagen IV [5,6]. Tubulointerstitial kidney disease is also mentioned in the literature as a rarer but sometimes the first manifestation of light chain deposition disease. Most often, deposits of light chains are seen along the tubular basement membrane, along with linear glomerular and vascular deposits [7]. Rarely, aggregates of light chains and Tamm Horsfall protein can lead to

mogu biti detektovane i svetlosnom mikroskopijom, zlatni standard dijagnoze predstavlja elektronska mikroskopija [10]. Na preparatima pod elektronskim mikroskopom mogu se videti sitni granulirani gusti depoziti u svim delovima bubrega. U zidu glomerulskih kapilara depoziti formiraju tanku traku prema lamini rara interna, a veći depoziti se gomilaju u subendotelijalnom regionu. Depoziti se mogu videti i spolja od tubularne bazalne membrane [10].

Što se tiče patofiziološkog mehanizma oštećenja drugih organa u bolesti deponovanja lakih lanaca, najčešće su opisivane promene na biopsijama jetre i srca, koje pokazuju taloženja amorfnih agregata u vaskularnim strukturama [11]. Na preparatima biopsije jetre viđeni su masivni homogeni eozinofilni infiltrati, koji su uglavnom locirani perisinusoidalno. Infiltrati se boje pozitivno na PAS bojenje, ali negativno na Kongo crvenu boju [12]. Biopsije srca uglavnom ne pokazuju promene na svetlosnoj mikroskopiji, dok se na eletronskoj mikroskopiji vide karakteristični linearni depoziti u intresticijalnom prostoru, u vidu tamnih granuliranih gustih depozita, koji su imunofluorescentnim bojenjem dokazani kao monoklonski laki lanci [11].

Prisustvo monoklonskih lakih lanaca u serumu, iako može biti idiopatsko, češće je udruženo sa nekih drugim oboljenjima limfocita i plazmocita, najčešće multiplim mijelomom, limfoplazmocitnim limfomom ili drugim ređim plazmocitnim diskrazijama. Prema literaturnim podacima ova bolest se nalazi udružena sa multiplim mijelomom u oko 65% slučajeva, makroglobulinemijom (oko 2%), i drugim limfoproliferativnim oboljenjima (2-3%) [13]. Takođe u sklopu monoklonske gamapatije nepoznatog značaja (MGUS), bolest deponovanja lakih lanaca se može manifestovati u organima u čak 32-85% slučajeva. Učestalost idiopatskog oblika bolesti deponovanja lakih lanaca nije utvrđena [14].

KLINIČKA SLIKA I LABORATORIJSKI NALAZI

Kliničkom slikom bolesti deponovanja lakih lanaca dominiraju simptomi i znaci zahvaćenog organa. Prema literaturnim podacima, najčešće zahvaćen organ je bubreg, kod oko 85% pacijenata [14]. Kod oko 35% pacijenata, zahvatanje bubrega nije jedina lokalizacija, te se uz bubrežne poremećaje javljaju i simptomi i znaci zahvatanja drugih organa. Izolovane ekstrarenalne manifestacije uz očuvanu bubrežnu funkciju retko su prisutne [4]. Zahvatanje drugih ograna najčešće podrazumeva zahvaćenost jetre (oko 23% slučajeva), zahvaćenost srca, pluća, perifrenog i centralnog nervnog sistema, kože, gastrointestinalnog trakta, slezine, štitaste žlezde i drugih [12,15-20].

distal tubule obstruction and acute renal failure [8,9]. Although changes in renal structures can be detected by light microscopy, the gold standard of diagnosis is electron microscopy [10]. On preparations under the electron microscope, small, granular, dense deposits can be seen in all kidney parts. In the wall of the glomerular capillaries, deposits form a thin strip towards the lamina rara interna, and larger deposits accumulate in the subendothelial region. Deposits can also be seen outside the tubular basement membrane [10].

As for the pathophysiological mechanism of damage to other organs in light chain deposition disease, the most frequently described changes in liver and heart biopsies show the deposition of amorphous aggregates in vascular structures [11]. Liver biopsy samples showed massive homogeneous eosinophilic infiltrates, mainly located perisinusoidally. Infiltrates stain is positive for PAS staining but negative for Congo red [12]. Heart biopsies generally show no changes on light microscopy, while electron microscopy shows characteristic linear deposits in the interstitial space in the form of dark granular dense deposits, proven by immunofluorescence staining to be monoclonal light chains [11].

Although it can be idiopathic, the presence of monoclonal light chains in the serum is more often associated with some other diseases of lymphocytes and plasma cells, most often multiple myeloma, lymphoplasmacytic lymphoma, or other rarer plasmacytic dyscrasias. According to literature data, this disease is associated with multiple myeloma in about 65% of cases, macroglobulinemia (about 2%), and other lymphoproliferative diseases (2-3%) [13]. Also, as part of monoclonal gammopathy of unknown significance (MGUS), light chain deposition disease can manifest in organs in as many as 32-85% of cases. The frequency of the idiopathic form of light chain deposition disease has not been determined [14].

CLINICAL PICTURE AND LABORATORY FINDINGS

The symptoms and signs of the affected organ dominate the clinical picture of light chain deposition disease. According to literature data, the most frequently affected organ is the kidney in about 85% of patients [14]. In about 35% of patients, involvement of the kidneys is not the only localization, and symptoms and signs of involvement of other organs appear along with kidney disorders. Isolated extrarenal manifestations with preserved renal function are rarely present [4]. Involvement of other branches most often involves involvement of the liver (about 23% of cases), involvement of the heart, lungs, peripheral and central nervous system, skin, gastrointestinal tract, spleen, thyroid gland, and others [12,15-20].

Tabela 1. Najčešće zahvaćeni organi u bolesti deponovanja lakih lanaca sa prikazom simptoma, znakova bolesti i nalaza dodatnih dijagnostičkih procedura

Organ/Sistem organa	Simptomi i znaci	Laboratorijske analize/dijagnostički nalazi
Bubreg	Povišen krvni pritisak, testasti otoci, umor, malaksalost	Povišene vrednosti uree, kreatinina, proteinurija (nefritičkog ili nefrotskog ranga), nalaz cilindara u urinu, pozitivni Bence-Jones protein / Biopsija bubrega
Srce	Uvećanje srca, restriktivna kardiomiopacije, srčana insuficijencija	Povišene vrednosti Moždanog natriuretskog peptida (proBNP), kao i troponina I, izmene elektorkardiograma (srčana hipertrofija) i ehokardiograma / Biopsija srca
Pluća	Restriktivni plućni poremećaj, dispnea, hemoptizije, bol u grudima	Restriktivan nalaz spirometrije, na multislajs kompjuterizovanoj tomografiji (MSCT) specifičan nalaz intersticijumskih promena u vidu čvoriča, cista
Jetra	Hepatomeglija, insuficijencija jetre, portalna hipertenzija	Povišene vrednosti AST, ALT, GGT, ALP, bilirubin, LDH, Ultrazvuk stomaka / Biopsija jetre
Slezina	Splenomegalija, bol pod levim rebarnim lukom	Ultrazvuk stomaka
Nervni sistem	Periferna polineuropatija, senzorna neuropatija, disfunkcija autonomnog nervnog sistema	Elektromioneurografija / Opciono biopsija nerva
Koža	Bulozne kožne promene, sitnozrnasti osip	Biopsija kože
Štitaste žlezda	Uvećanje štitaste žlezde	Visoke vrednosti tireostimulišućeg hormona (TSH), niže vrednosti tireoidnih hormona (fT4, T3) / Ultrazvuk štitaste žlezde

Table 1. The most frequently affected organs in light chain deposition disease with a presentation of symptoms, signs of the disease, and findings of additional diagnostic procedures

Organ/Organ system	Symptoms and signs	Laboratory analyses/diagnostic findings
Kidney	High blood pressure, swelling, fatigue, weakness	Increased values of urea, creatinine, proteinuria (nephritic or nephrotic grade), finding of cylinders in urine, positive Bence-Jones protein / Kidney biopsy
Heart	Enlargement of the heart, restrictive cardiomyopathy, heart failure	Elevated values of Brain natriuretic peptide (proBNP), as well as troponin I, electrocardiogram (cardiac hypertrophy) and echocardiogram changes / Heart biopsy
Lungs	Restrictive pulmonary disorder, dyspnea, hemoptysis, chest pain	Restrictive finding of spirometry, on multislice computed tomography (MSCT) specific finding of interstitial changes in the form of nodules, cysts
Liver	Hepatomegaly, liver failure, portal hypertension	Elevated values of AST, ALT, GGT, ALP, bilirubin, LDH, Abdominal ultrasound / Liver biopsy
Spleen	Splenomegaly, pain under the left rib cage	Abdominal ultrasound
Nervous system	Peripheral polyneuropathy, sensory neuropathy, autonomic nervous system dysfunction	Electromyoneurography / Optional nerve biopsy
Skin	Bullous skin changes, fine-grained rash	Skin biopsy
Thyroid gland	Enlargement of the thyroid gland	High values of thyroid-stimulating hormone (TSH), low values of thyroid hormones (fT4, T3), / Ultrasound of the thyroid gland

DIJAGNOSTIKA

Postavljanje dijagnoze bolesti taloženja lakih lanaca sastoji se iz nekoliko koraka. Ukoliko se na osnovu kliničke slike i manifestacija bolesti postavi sumnja na bolest lakih lanaca, prvi korak je svakako biopsija zahvaćenog organa, najčešće bubrega, ali i jetre, srca, pluća, kože, nerava [21]. Na patohistološkom preparatu vide se amorfni linearni depoziti lakih lanaca, a

DIAGNOSTICS

Diagnosing light chain deposition disease consists of several steps. If light chain disease is suspected based on the clinical picture and manifestations of the disease, the first step is a biopsy of the affected organ, most often the kidneys, but also the liver, heart, lungs, skin, and nerves [21]. Amorphous linear deposits of light chains can be seen on the pathohistological

negativnim bojenjem na Kongo crveno isključuje se amiloidoza lakih lanaca [7]. Potvrda da je zaista reč o monoklonskim lakim lancima sprovodi se određivanjem koncentracije lakih lanaca u serumu i urinu, zajedno sa elektroforezom i imunoelektroforezom proteina seruma i urina. Na ovim ispitivanjima potvrđuje se da su laki lanci monoklonalni, ali se ispituje i da li je reč samo o lakim lancima ili se oni kao paraprotein sintetišu uz teške lance [22]. Poslednji korak u dijagnostici predstavlja i ispitivanje koštane srži patohistološkom analizom, gde se detektuje broj plazmocita, ali i njihove karakteristike na imunohistohemijskom bojenju i fluorescentnoj in situ hibridizaciji (FISH) [4,21,23]. Alternativno, protočnom citometrijom u aspiratu koštane srži mogu se ispitati imunofenotipske karakteristike plazmocita [2,4,21].

TOK, PROGNOZA I LEČENJE

Bolest taloženja lakih lanaca pokazuje prirodno progresivni tok sa krajnjim gubitkom funkcije zahvaćenog organa [24]. Kod skoro 70% pacijenta obolelih od bolesti taloženja lakih lanaca postoji udruženost sa plazmocitnom diskrazijom (najčešće multiplim mijelomom) ili nekim drugim limfoproliferativnim oboljenjem [13]. Prognozni parametri koji utiču na dalji tok bolesti su starost pacijenta, prisutnost drugih plazmocitnih diskrazija ili limfoproliferativne bolesti, kao i prisustvo ekstrarenalnog oboljenja, što predstavlja značajan negativan prognozni parametar [24]. Ukoliko razmatramo bubrežne prognozne parametre, najveći značaj ima brzina razvoja bubrežne insuficijencije, dok se kod zahvatanja srca prate biohemijski parametri kao što su proBNP i troponin I [25].

Lečenje ovog entiteta, ukoliko je udružen sa multiplim mijelomom ili drugim plazmocitnim limfoproliferativnim bolestima, lečimo prema protokolima za lečenje tih bolesti. Kada je reč o idiopatskom obliku, ne postoje zvanični konsenzusi o terapiji [26]. U literaturi se uglavnom pominju male grupe lečenih pacijenata, a kontrolisane studije, zbog retkosti entiteta, nisu sprovođene. Prema dostupnim literaturnim podacima, pacijenti su uglavnom lečeni protokolima baziranim na terapijama za lečenje multiplog mijeloma, uz potporu visokodoznom hemioterapijom i autologom transplantacijom matičnih ćelija. Procena efekta lečenja zasniva se na postizanju hematološkog odgovora (procena monoklonskih plazmocita u kostnoj srži), merenju koncentracije slobodnih lakih lanaca u serumu, kao i praćenju funkcije zahvaćenog organa [14,26].

Lečenje pacijenata je inicijalno bazirano na primeni kortikosteroidne terapije, koja je kod prvih dokazanih slučajeva primenjivana najpre kao mono-

preparation, and light chain amyloidosis is ruled out by negative Congo red staining [7]. Confirmation that it is indeed monoclonal light chains is carried out by determining the concentration of light chains in serum and urine, together with serum and urine protein electrophoresis and immunoelectrophoresis. These tests confirm that the light chains are monoclonal, but whether it is only about the light chains or whether they are synthesized as a paraprotein along with the heavy chains [22] is also examined. The last step in the diagnosis is the examination of the bone marrow by pathohistological analysis, where the number of plasma cells is detected, as well as their characteristics on immunohistochemical staining and fluorescent in situ hybridization (FISH) [4,21,23]. Alternatively, immunophenotypic characteristics of plasma cells can be examined by flow cytometry in bone marrow aspirate [2,4,21].

COURSE, PROGNOSIS, AND TREATMENT

Light chain deposition disease shows a naturally progressive course with eventual loss of function of the affected organ [24]. In almost 70% of patients suffering from light chain deposition disease, there is an association with plasmacytic dyscrasia (most often multiple myeloma) or some other lymphoproliferative disease [13]. Prognostic parameters that affect the further course of the disease are the age of the patient, the presence of other plasmacytic dyscrasias or lymphoproliferative diseases, as well as the presence of extrarenal disease, which represents a significant negative prognostic parameter [24]. If we consider renal prognostic parameters, the speed of development of renal insufficiency has the most significant importance, while in the case of cardiac involvement, biochemical parameters such as proBNP and troponin I are monitored [25].

The treatment of this entity, if it is associated with multiple myeloma or other plasmacytic lymphoproliferative diseases, is treated according to the protocols for treating these diseases. When it comes to the idiopathic form, there are no official consensuses on therapy [26]. Small groups of treated patients are primarily mentioned in the literature, and controlled studies have not been conducted due to the entity's rarity. According to available literature data, patients were mostly treated with protocols based on therapies for the treatment of multiple myeloma, supported by high-dose chemotherapy and autologous stem cell transplantation. The assessment of the effect of treatment is based on achieving a hematological response (estimation of monoclonal plasma cells in the bone marrow), measuring the concentration of free light chains in the serum, as well as monitoring the function of the affected organ [14,26].

terapija, sa postizanjem efekta stabilizacije funkcije zahvaćenog organa i postizanjem parcijalnog hematološkog terapijskog odgovora [23]. Osim kortikosteroidne terapije, kao monoterapija, primenjivani su i kombinovani hemioterapijski režimi sa vinkristinom, adriablastinom (VAD) ili vinkristinom, melfalanom i ciklofosfamidom (VMCP) [5,23]. Nakon toga najpre je uz kortikosteroidnu terapiju primenjivana i terapija talidomidom sa ili bez ciklofosfamida, kod manjeg broja pacijenata. Podaci o efikasnosti ove terapije uglavnom su bazirani na pojedinačnim prikazima slučajeva, gde detektujemo kako refrakternost na terapiju, tako i postizanje kompletne dugotrajne remisije [27,28].

Najveći broj pacijenata, prema literaturi je do sada lečen protokolima baziranim na bortozomibu, i to bortezomib+ciklofosfamid+deksametazon (VCD) ili bortezomib+deksametazon (VD), sa postizanjem dobrog hematološkog odgovora. Kompletan odgovor (CR) postignut je kod oko 55,6%, a veoma dobar parcijalni odgovor (VGPR) i parcijalni odgovor (PR) kod ostalih tretiranih pacijenata [26]. Primena autologne transplantacije u lečenju ovih pacijenata nakon inicijalnog lečenja dovodi do dugotrajnije i stabilnije remisije, s povećanjem kompletnog odgovora na 61,5% pacijenata [20].

Lečenje bolesti deponovanja lakih lanaca sprovođeno je i kod pojedinačnih slučajeva uz primenu terapijskih modaliteta sa lenalidomidom. Literaturni podaci govore o većem broju različitih terapijskih režima, te je lenalidomid korišćen u kombinaciji sa prednizonom, sa deksametazonom, melfalanom i prednizonom, kao i dekstametazonom i ciklofosfamidom. Postignuti efekti su zabeleženi kao PR ili VGPR, uz održavanje odgovora od 1-4 godine [29].

Poslednjih godina pojavljuju se podaci o pacijentima lečenim daratumumabom kao monoterapijom u inicijalnom lečenju, kod kojih se postiže i održava dugotrajna hematološka remisija [30]. Daratumumab je posmatran i u formi konsolidacije nakon lečenja protokolima baziranim na bortezomibu, gde je kod svih pacijenata zabeleženo poboljšanje hematološkog odgovora (iz PR u VGPR, odnosno iz VGPR u CR) [31].

Kao potporna terapija kod ovih pacijenata pominje se i transplantacija zahvaćenog organa kod terminalne insuficijencije, ali je za sprovođenje ove procedure neophodno prethodno postizanje hematološkog odgovora i smanjenje koncentracije lakih lanaca u serumu, jer u suprotnom dolazi do ponovnog oštećenja funkcije transplantiranog organa [32].

The treatment of patients was initially based on the application of corticosteroid therapy, which in the first proven cases was applied as monotherapy, stabilizing the affected organ's function and achieving a partial hematological therapeutic response [23]. In addition to corticosteroid therapy, combined chemotherapy regimens with vincristine, adriablastin (VAD), or vincristine, melphalan, and cyclophosphamide (VMCP) were used as monotherapy [5,23]. After that, therapy with thalidomide with or without cyclophosphamide was first applied in addition to corticosteroid therapy in a smaller number of patients. Data on the effectiveness of this therapy are mainly based on individual case reports, where we detect both refractoriness to treatment and the achievement of complete long-term remission [27,28].

The largest number of patients, according to the literature, have so far been treated with bortezomib-based protocols, namely bortezomib+cyclophosphamide+dexamethasone (VCD) or bortezomib+-dexamethasone (VD), achieving a good hematological response. Complete response (CR) was achieved in about 55.6%, and very good partial response (VGPR) and partial response (PR) in other treated patients [26]. The use of autologous transplantation in treating these patients after the initial treatment leads to a longer and more stable remission, with an increase in complete response to 61.5% of patients [20].

Treatment of light chain deposition disease was also carried out in individual cases using therapeutic modalities with lenalidomide. Literature data speak of many different therapeutic regimens, and lenalidomide was combined with prednisone, dexamethasone, melphalan, and prednisone, as well as dexamethasone and cyclophosphamide. The achieved effects were recorded as PR or VGPR, with response maintenance of 1-4 years [29].

In recent years, data have appeared on patients treated with daratumumab as monotherapy in the initial treatment, in whom long-term hematological remission is achieved and maintained [30]. Daratumumab was also observed in consolidation after treatment with protocols based on bortezomib, where the hematological response was improved in all patients (from PR to VGPR or from VGPR to CR) [31].

Transplantation of the affected organ in case of terminal insufficiency is also mentioned as a supportive therapy in these patients, but in order to carry out this procedure, it is necessary to achieve a hematological response and reduce the concentration of light chains in the serum, because otherwise the function of the transplanted organ will be damaged again [32].

ZAKLJUČAK

Bolest deponovanja lakih lanaca predstavlja redak entitet i dijagnostički izazov kod većine obolelih pacijenata. Za sprovođenje adekvatne dijagnostike, praćenja i terapije pacijenata potreban je multidisciplinarni pristup koji obuhvata nefrologa, hematologa, patologa, kao i subspecijalista drugih grana kod ekstrarenalnih manifestacija.

Sukob interesa: Nije prijavljen.

CONCLUSION

Light chain deposition disease is a rare entity and diagnostic challenge in most affected patients. A multidisciplinary approach, including nephrologists, hematologists, pathologists, and subspecialists of other branches in case of extrarenal manifestations, is needed to carry out adequate diagnostics, follow-up, and therapy of patients.

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