Reumatizam 2022;69(2):110–116
https://doi.org/10.33004/reumatizam-69-2-4

CASE REPORT PRIKAZ BOLESNIKA

EARLY CYCLOPHOSPHAMIDE TREATMENT IN NEW-ONSET PROGRESSIVE CUTANEOUS SYSTEMIC SCLEROSIS – A CASE REPORT AND LITERATURE REVIEW

RANA PRIMJENA CIKLOFOSFAMIDA U LIJEČENJU NOVONASTALE PROGRESIVNE KOŽNE SISTEMSKE SKLEROZE – PRIKAZ BOLESNIKA I PREGLED LITERATURE

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Received / Primljeno: 14th September 2022 / 14. 9. 2022.
Accepted / Prihvaćeno: 4th December 2022 / 4. 12. 2022.

Abstract

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by fibrosis of the skin and internal organs. Treatment of SSc remains a challenge, as it depends on disease extent, pattern and organ involvement. The use of cyclophosphamide (CYC) is mainly recommended for treatment of SSc interstitial lung disease, however its efficacy on skin involvement in SSc has been demonstrated by several studies. We present a case of a patient with new-onset progressive cutaneous diffuse SSc, who was successfully treated with a three-month course of CYC. Significant improvement of skin fibrosis was recorded, as well as a favourable disease outcome in the five-year follow up period. A brief literature review is also presented, demonstrating that CYC can be an effective and safe first-line treatment option in similar cases.

Key words: systemic sclerosis, cyclophosphamide, skin

Sažetak

Sistemska skleroza (SSc) je kronična autoimunosna bolest koju karakterizira fibroza kože i unutarnjih organa. Liječenje SSc-a izazov je za liječnika jer izbor terapije ovisi o proširenosti i obrascu bolesti, kao i zahvaćenosti unutarnjih organa. Upotreba ciklofosfamida (CYC) većinom je preporučena za liječenje intersticijske plućne bolesti u SSc-u. Međutim, njegova učinkovitost u liječenju kožnih manifestacija SSc-a dokazana je u više istraživanja. Prikazujemo slučaj bolesnice s novonastalom progresivnom, difuznom kožnom SSc, koja je uspješno liječena upotrebom CYC-a tijekom tri mjeseca. Zabilježeno je značajno poboljšanje kožne fibroze, kao i povoljan ishod bolesti tijekom idućih pet godina praćenja. Prikazan je i kraći pregled literature koji govori u prilog tomu da CYC može biti učinkovita i sigurna prva linija liječenja u sličnim slučajevima.

Ključne riječi: sistemska skleroza, ciklofosfamid, koža

INTRODUCTION

Systemic sclerosis (SSc) is a rare chronic autoimmune disease which causes diffuse fibrosis of the skin and internal organs and is also characterized by vascular wall damage and disfunction of innate and acquired immunity (1). The specific manifestations of SSc are the result of different, distinct processes, such as cell-mediated autoimmunity due to innate and acquired immune system abnormalities, vasculopathy of small vessels and excessive accumulation of matrix components in skin, blood vessels and internal organs (2). The hallmark of the disease is skin involvement –i.e. skin thickening, which can be estimated using the modified Rodnan skin score (mRSS), which is a validated standard method (3,4). Two subsets of disease are generally recognized, depending on the pattern of skin involvement – limited and diffuse SSc. In limited SSc, skin thickening is limited to the face and distal extremities, whereas in the diffuse form skin changes are widespread and involve the trunk and proximal extremities (1). Greater extent of skin involvement has been linked to poorer outcomes, more severe internal organ manifestations and disability (4). SSc may also affect internal organs by causing interstitial and perivascular fibrosis, resulting in disfunction of the gastrointestinal (GI) tract, diffuse pulmonary fibrosis, cardiac abnormalities, pulmonary hypertension and renal involvement, among others. Organ involvement is reported to be earlier and more severe in diffuse SSc (5). Diagnosis of the disease is made by clinical evaluation, as well as testing for specific autoantibodies, such as anticentromere, anti-topoisomerase III (anti-SCL-70) and anti-RNA polymerase III antibodies (5). The 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria also aid in diagnosis (6). Modality of treatment depends on the pattern, organ involvement and extent of the disease and still remains a challenge for physicians (1). Treatment options include several modalities, including different forms of symptomatic therapy. Disease-modifying antirheumatic drugs such as methotrexate, can be used to treat skin fibrosis and arthritis in SSc (7,8). Treatment aimed specifically at skin involvement has been evaluated in several observational and clinical trials, which suggest favourable outcomes with the use of all of the following: methotrexate, cyclophosphamide (CYC), mycophenolate mofetil, cyclosporin, D-penicillamin, intravenous immunoglobulins (IVIG), rituximab and others (5). However, EULAR recommendations on SSc treatment only suggest MTX could be considered for treatment of skin manifestations in diffuse SSc (7). CYC, an alkylating agent, acts as a cytotoxic immunosuppressant by lymphocyte modulation, thereby abrogating inflammation and fibrosis (9). Treatment guidelines generally recommend

UVOD

Sistemska skleroza (SSc) je rijetka kronična autoimunosna bolest koja uzrokuje difuznu fibrozu kože i unutarnjih organa, a neke od njenih karakteristika također su oštećenje vaskularne stijenke i poremećaj urođene i stečene imunosti (1). Specifične manifestacije SSc-a rezultat su različitih procesa, kao što je autoimunost posredovana stanicama zbog urođenih i stečenih abnormalnosti imunološkog sustava, vaskulopatija malih krvnih žila i prekomjerno nakupljanje komponenti matriksa u koži, krvnim žilama i unutarnjim organima (2). Jedno od obilježja bolesti jest zahvaćenost kože, to jest, zadebljanje kože, koje se može procijeniti pomoću modificiranoga Rodnanovog kožnog testa (engl. *Modified Rodnan skin score*, mRSS) koji je provjerena standardna metoda procjene kožne zahvaćenosti (3,4). Općenito se prepoznaju dvije podgrupe bolesti, ovisno o obrascu zahvaćenosti kože – ograničena i difuzna SSc. U ograničenoj SSc zadebljanje kože ograničeno je na lice i distalne ekstremitete, dok su u difuznom obliku bolesti kožne promjene proširene na veći dio tijela i zahvaćaju trup i proksimalne ekstremitete (1). Veći opseg zahvaćenosti kože povezan je s lošijim ishodima, težim manifestacijama unutarnjih organa i invaliditetom (4). SSc također može utjecati na unutarnje organe uzrokujući intersticijsku i perivaskularnu fibrozu, što, između ostalog, dovodi do disfunkcije gastrointestinalnog (GI) trakta, difuzne plućne fibroze, srčanih abnormalnosti, plućne hipertenzije i zahvaćenosti bubrega. Zahvaćenost organa javlja se ranije i u težem obliku kod difuzne SSc (5). Dijagnoza bolesti postavlja se kliničkom procjenom, kao i testiranjem na specifična autoantitijela, kao što su anticentromera antitijela, anti-topoizomeraza III (anti-SCL-70) i anti-RNA polimeraza III antitijela (5). Klasifikacijski kriteriji reumatoloških društava American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) iz 2013. također pomažu u dijagnozi ove bolesti (6). Modalitet liječenja ovisi o obrascu, zahvaćenosti organa i proširenosti bolesti te i dalje predstavlja izazov za liječnike (1). Mogućnosti liječenja uključuju nekoliko modaliteta, uključujući različite oblike simptomatske terapije. Antireumatski lijekovi koji modificiraju tijek bolesti, kao što je metotreksat, mogu se primjenjivati za liječenje kožne fibroze i artritisa u SSc-u (7,8). Liječenje usmjereno posebno na zahvaćenost kože procijenjeno je u nekoliko opservacijskih i kliničkih ispitivanja, koja sugeriraju povoljne ishode uz korištenje svih lijekova u nastavku: metotreksat, ciklofosfamid (CYC), mikofenolat mofetil, ciklosporin, D-penicilamin, intravenski imunoglobulini (IVIG), rituksimab i drugi (5). Međutim, preporuke EULAR-a o liječenju SSc-a samo sugeriraju da bi se MTX mogao uzeti u obzir za liječenje kožnih manifestacija kod difuzne SSc (7). CYC, alkilirajući agens, djeluje kao citotoksični imunosupresiv modulacijom limfocita, čime uklanja simptome upale i fibroze (9).

its use for SSc interstitial lung disease, however its efficacy on skin involvement in SSc has been demonstrated by several studies (7,10). Hereby we present a case of a patient with new-onset progressive diffuse systemic sclerosis, which predominantly manifested with skin fibrosis and was successfully treated with a three-month course of CYC.

CASE REPORT

A 59-year-old woman presented to our Rheumatology and Clinical Immunology outpatient clinic with progressive tightening, thickening and hardening of the skin, which started approximately 6 months prior. The changes were also accompanied by sensations such as skin itching, dryness and burning. The skin changes first appeared on the abdomen and subsequently spread to the chest, neck, back and limbs (forearms and lower legs), corresponding to a modified Rodnan skin score (mRSS) of 13/51. There were also areas of hyperpigmentation and purple-coloured spots on her forearms and lower legs initially suspect of livedo reticularis. She also reported discomfort in her hand joints and excessive fatigue, as well as occasional hoarseness. Her medical history was unremarkable, containing only nephrolithiasis and ocular hypertension. The patient's body weight was 88 kg. Laboratory findings showed positive antinuclear antibodies (with a titre of >1:640), subtly positive anti-double-stranded DNA of 23U/ml (n.v. <20U/ml) and positive anti-centromere antibodies as well as moderately elevated C-reactive protein levels (13.8mg/L, n.v. <5mg/L). A skin biopsy showed sclerotic changes of dermal collagen, proliferation of fibroblasts, as well as perivascular lymphocytic infiltrates. Capillaroscopy showed no abnormalities specific for SSc. The patient was also evaluated for lung involvement – spirometry and diffusing capacity for carbon monoxide (DLCO) were within normal limits. A CT scan of the thorax and abdomen showed no specific lung abnormalities, as well as no sign of underlying malignancy in the lungs or other organs. However, multiple cysts were found in both kidneys, because of which the patient was evaluated by a nephrologist, however this finding had no effect on kidney function and was deemed likely not SSc-related. Heart involvement was evaluated by echocardiography, which showed 1st degree diastolic dysfunction of the left ventricle and subtle mitral and tricuspid regurgitation but showed no signs of pulmonary hypertension. Ultrasound (US) examination of hand and foot joints showed no active joint inflammation. Additionally, esophagogastroduodenoscopy (EGDS) showed incompetence of the gastric cardia, a hiatal hernia and gastritis. Because of patient-reported hoarseness, she was also evaluated by an otorhinolaryngologist, who diagnosed her with vocal cord edema and nodules.

Smjernice za liječenje općenito preporučuju njegovu upotrebu za intersticijsku bolest pluća u sistemskoj sklerozi (SSc), međutim njegova učinkovitost na zahvaćenost kože kod SSc-a dokazana je u nekoliko istraživanja (7,10). U ovom istraživanju prikazujemo slučaj bolesnice s novonastalom progresivnom, difuznom sistemskom SSc, koja se manifestirala u obliku kožne fibroze i koja je uspješno liječena upotrebom CYC-a tijekom razdoblja od tri mjeseca.

PRIKAZ BOLESNICE

U naš Zavod za kliničku imunologiju, alergologiju i reumatologiju javila se 59-godišnja žena sa simptomima progresivnog zatezanja, zadebljanja i otvrdnuća kože koji su se počeli javljati prije otprilike šest mjeseci. Promjene su također bile praćene osjećajima poput svrbeža, suhoće i peckanja kože. Kožne promjene prvo su se pojavile na trbuhu, a zatim su se proširile na prsa, vrat, leđa i udove (podlaktice i potkoljenice), što odgovara rezultatu modificiranoga Rodnanovog kožnog testa (mRSS) od 13/51. Na koži su također bila prisutna područja hiperpigmentacije i ljubičaste mrlje na podlakticama i potkoljenicama za koje se u početku sumnjalo da su livedoidni vaskulitis (*livedo reticularis*). Bolesnica je također prijavila nelagodu u zglobovima ruku i pretjerani umor, kao i povremenu promuklost. Njezina povijest bolesti bila je bez većih abnormalnosti, sadržavala je samo nefrolitijazu i očnu hipertenziju. Tjelesna težina bolesnice bila je 88 kg. Laboratorijski nalazi pokazali su pozitivna antinuklearna protutijela (s titrom >1:640), blago pozitivna antitijela na dvostruku uzvojnicu DNA od 23 jedinica/ml (normalna vrijednost <20 jedinica/ml) i pozitivna anticentromerna protutijela kao i umjereno povišene razine C-reaktivnog proteina (13,8 mg/L, normalna vrijednost <5mg/L). Biopsija kože pokazala je sklerotične promjene dermalnog kolagena, proliferaciju fibroblasta, kao i perivaskularne limfocitne infiltrate. Kapilaroskopija nije pokazala abnormalnosti karakteristične za SSc. Bolesnici je također procijenjena zahvaćenost pluća: spirometrija i difuzijski kapacitet za ugljikov monoksid (DLCO) bili su u granicama normale. CT toraksa i abdomena nije pokazao specifične abnormalnosti pluća, kao ni znakove podležećega malignog tumora u plućima ili drugim organima. Međutim, pronađene su višestruke ciste na oba bubrega, zbog čega je bolesnica upućena na pregled kod nefrologa, no ovaj nalaz nije utjecao na funkciju bubrega i smatra se da vjerojatno nije povezan sa SSc-om. Zahvaćenost srca procijenjena je ehokardiografijom, koja je pokazala dijastoličku disfunkciju lijevog ventrikula prvog stupnja i suptilnu mitralnu i trikuspidalnu regurgitaciju, ali nije pokazala znakove plućne hipertenzije. Ultrazvuk (UZV) zglobova šake i stopala nije pokazao aktivnu upalu zglobova. Uz to, ezofagogastroduodenoskopija (EGDS) pokazala je inkompetentnost želučane kardije, hijatalnu herniju i gastritis. Zbog pro-

Following initial evaluation, the patient was diagnosed with progressive systemic sclerosis.

A three-month course of bi-weekly 500mg intravenous CYC was elected as treatment of choice, which corresponds to a total of 3g iv CYC divided in 6 doses – also known as the Euro – Lupus protocol (11). An antiemetic (ondansentron), an urotoxicity-preventing agent (mesna) and prophylactic antibiotic were administered regularly in the course of CYC treatment. The treatment course was carried out without complications or serious side effects. Two weeks after the finished treatment course, skin changes showed improvement in all affected areas and maintenance treatment with methotrexate (MTX) was started in a weekly dose of 10mg p.o. Increase of MTX dosage could not be sustained due to patient-reported side effects (nausea, headaches). On subsequent evaluation, approximately six months after treatment with CYC, further improvement of skin changes was evident, with physical examination showing only linear skin changes on the abdomen and hypo- and hyperpigmented spots on the lower extremities, with a decrease of the mRSS, which was 8/51. This corresponds to a mRSS decrease of 5 points or 38.5%. Both mRSS measurements were performed by the patient's rheumatologist-immunologist. Patient-reported symptoms had also significantly decreased, with no newly formed skin changes, no Raynaud's phenomenon or skin ulcerations. In the following 5 years, the patient has received regular follow-up examinations, during which there were no signs of recurrence or progression of skin lesions and the patient reported general well-being with no signs of Raynaud's phenomenon or digital swelling and ulcerations. She reported dysphagia, which was self-limiting. Approximately 1 year after initiation of therapy, the patient stopped taking MTX due to elevated liver enzymes and recurring headaches and did not consent to further immunosuppressive treatment. However, she reported improvement in skin changes up to 1.5 years after CYC treatment. Approximately five years after CYC treatment, laboratory findings still showed positive antinuclear antibodies (with a titre of >1:640) and positive anti-centromere antibodies, however with negative anti-double-stranded DNA and Scl-70 antibodies. Follow-up examinations remain without signs of disease relapse or pulmonary hypertension, interstitial (or other) lung disease, kidney disfunction, or progression of upper gastrointestinal tract changes; echocardiography findings remain without significant changes.

DISCUSSION

This clinical case report highlights CYC as a significantly effective treatment option in early, diffuse cutaneous SSc. Although there are no established mRSS response criteria, both of the most used criteria in lit-

muklosti koju je prijavila bolesnica pregledao ju je i otorinolaringolog, koji joj je dijagnosticirao edem glasnica i čvoriće glasnica. Nakon početne procjene, bolesnici je dijagnosticirana progresivna sistemska skleroza.

Primjena doze od 500 mg CYC-a intravenski u dvotjednim razmacima tijekom razdoblja od tri mjeseca bila je odabrana metoda liječenja, što odgovara primjeni doze od 3 g CYC-a intravenski, podijeljenoj u 6 doza (pulseva), što je također poznato kao Eurolupus protokol (ELN) (11). Tijekom liječenja primjenom CYC-a redovito su primjenjivani antiemetik (ondansentron), lijek za sprječavanje urotoksičnosti (mesna) i profilaktički antibiotik. Liječenje je proteklo bez komplikacija i teških nuspojava. Dva tjedna nakon završene kure liječenja u pogledu kožnih promjena bilo je vidljivo poboljšanje na svim zahvaćenim područjima i započeto je liječenje metotreksatom (MTX) u tjednoj dozi od 10 mg perioralno. Povećanje doze MTX-a nije bilo održivo zbog nuspojava koje je prijavila bolesnica (mučnina, glavobolje). Naknadnom procjenom, otprilike šest mjeseci nakon liječenja CYC-om, bilo je vidljivo daljnje poboljšanje kožnih promjena, s fizičkim pregledom koji je pokazao samo linearne kožne promjene na trbuhu i hipopigmentaciju i hiperpigmentaciju na donjim ekstremitetima, uz smanjenje rezultata mRSS-a, koji je iznosio 8/51. Taj rezultat odgovara smanjenju rezultata mRSS-a od 5 bodova ili 38,5%. Oba mRSS testa proveo je bolesničin reumatolog/imunolog. Simptomi koje je prijavila bolesnica također su se značajno smanjili, bez novonastalih promjena na koži, bez Raynaudovog sindroma ili kožnih ulceracija. U sljedećih pet godina bolesnica je bila na redovitim kontrolnim pregledima, tijekom kojih nije bilo znakova recidiva ili progresije kožnih lezija, a bolesnica je prijavila opće dobro stanje bez znakova Raynaudovog sindroma ili oticanja prstiju i ulceracija. Bolesnica je prijavila disfagiju, koja je bila samoograničavajuća. Otprilike godinu dana nakon početka terapije, bolesnica je prestala uzimati MTX zbog povišenih jetrenih enzima i ponavljajućih glavobolja te nije pristala na daljnje liječenje imunosupresivnom terapijom. Međutim, prijavila je poboljšanje promjena na koži u razdoblju do 1,5 godine nakon liječenja CYC-om. Otprilike pet godina nakon liječenja CYC-om, laboratorijski su nalazi i dalje pokazivali pozitivna antinuklearna protutijela (s titrom >1:640) i pozitivna anticentromerna protutijela, ali s negativnim antitijelima na dvostruku uzvojnicu DNA i Scl-70 protutijelima. Kontrolni pregledi i dalje su pokazivali nedostatak znakova relapsa bolesti ili plućne hipertenzije, intersticijske (ili druge) bolesti pluća, disfunkcije bubrega ili progresije promjena gornjeg gastrointestinalnog trakta, a ehokardiografski nalaz i dalje je bio bez značajnijih promjena.

RASPRAVA

Ovaj klinički prikaz bolesnice ističe CYC kao značajno učinkovitu opciju liječenja rane, difuzne kožne SSc. Iako ne postoje uspostavljeni kriteriji odgovora na mRSS, oba

erature to define meaningful change – a mRSS decrease of 5 points or 25% or more – were met in this case (12,13). Optimal SSc treatment remains challenging, as early diagnosis, correct assessment of disease progression, severity and organ involvement should be the most important guide in decisions about treatment (5,7). In the case of our patient, the extent and localization of skin thickening indicates a diffuse form of SSc, as well as the presence of polyarthralgia, which is more frequent in diffuse disease (14). Involvement of the GI tract and larynx presenting as mild dysphagia and dysphonia, with objective findings of gastric cardia incompetence, gastritis, vocal cord nodules and edema might be SSc manifestations, which can occur in both limited and diffuse disease(15,16). However, as these presented only with self-limiting dysphagia and occasional hoarseness, it is less likely they are SSc-related. Sings of possible initial heart involvement were also found, as diastolic dysfunction and valvular regurgitation are among the more common findings in both limited and diffuse SSc disease forms (17–19). Although it is worth noting that these findings are also likely to be age-related. However, anticentromere antibodies, which were present in our patient, are more indicative of limited disease; nevertheless, they can be found in 20–30% of overall SSc patients and have been reported in patients with the diffuse form of SSc (20,21). When applied to the patient in this case, the aforementioned ACR/EULAR classification criteria were not met, however the use of classification criteria is recommended for including patients in epidemiological, clinical or experimental studies and should not deter decision making based on clinical experience or delay treatment initiation (6). Optimal decisions about treatment of choice are challenging, as existing research on effectiveness of different therapeutic options is still mainly not double blinded and placebo controlled, with varying levels of evidence (5,22). There is a high unmet need for highly effective, disease-modifying therapies with manageable toxicity profiles (9). Treatment guidelines have been published and updated in 2016 by EULAR, which state that MTX might be considered as treatment for skin involvement in early diffuse SSc, while the use of CYC should be considered in progressive lung disease (7). Since our patient was treated with MTX after CYC, its possible effects in the case of our patient cannot be excluded; although it is worth noting that treatment with MTX lasted less than a year. Furthermore, studies focusing on MTX treatment in SSc, reported no beneficial effects on organ involvement (23,24). However, results of multiple studies describe favourable effects of CYC on skin manifestations in diffuse cutaneous SSc. A number of observational trials, as well as clinical studies using CYC as a control, showed efficacy of CYC on skin involvement

kriterija koji se najčešće upotrebljavaju u literaturi za definiranje značajne promjene, to jest, smanjenje rezultata mRSS-a od 5 bodova ili za 25% ili više, ispunjena su u ovom prikazu bolesnice (12,13). Optimalno liječenje SSc-a i dalje predstavlja izazov, budući da bi rana dijagnoza, točna procjena progresije bolesti, težina bolesti i zahvaćenost organa trebali biti najvažnije smjernice u donošenju odluka o metodi liječenja (5,7). U slučaju naše bolesnice raširenost i lokalizacija zadebljanja kože ukazuju na difuzni oblik SSc-a, kao i na prisutnost poliartralgije koja je češća kod difuzne bolesti (14). Zahvaćenost GI trakta i grkljana koja se očituje kao blaga disfagija i disfonija, s objektivnim nalazima inkompetentnosti želučane kardije, gastritisom, čvorićima glasnica i edemom mogu biti manifestacije SSc-a, koje se mogu pojaviti i kod ograničenog i kod difuznog oblika bolesti (15,16). Međutim, budući da se one manifestiraju samo samoograničavajućom disfagijom i povremenom promuklošću, manje je vjerojatno da su povezane sa SSc-om. Također su pronađeni znakovi moguće početne zahvaćenosti srca, jer su dijastolička disfunkcija i valvularna regurgitacija među češćim nalazima u ograničenim i difuznim oblicima bolesti SSc (17–19). Uz to, bitno je napomenuti da su ti nalazi također vjerojatno povezani s dobi bolesnika. Međutim, anticentromerna protutijela, koja su bila prisutna u naše bolesnice, više ukazuju na ograničenu bolest, a usprkos tomu mogu se naći u 20–30% svih bolesnika sa SSc-om i zabilježeni su u bolesnika s difuznim oblikom SSc-a (20,21). U slučaju ove bolesnice, gore spomenuti kriteriji klasifikacije ACR/EULAR nisu bili ispunjeni, no uporaba kriterija klasifikacije preporučuje se za uključivanje bolesnika u epidemiološke, kliničke ili eksperimentalne studije i ne bi trebala spriječiti donošenje odluka na temelju kliničkog iskustva ili odgoditi početak liječenja (6). Optimalne odluke o odabiru metode liječenja izazovne su jer postojeća ispitivanja o učinkovitosti različitih opcija liječenja još uvijek uglavnom nisu dvostruko slijepa i kontrolirana placebom, s različitim razinama dokaza (5,22). Postoji velika neispunjena potreba za vrlo učinkovitim metodama liječenja koje modificiraju tijek bolesti s profilima toksičnosti koji se mogu kontrolirati (9). Smjernice za liječenje objavljene su i ažurirane 2016. od strane EULAR-a, a u njima se navodi da se MTX može uzeti u obzir kao metoda liječenja za zahvaćenost kože kod rane difuzne SSc, dok bi upotrebu CYC-a trebalo razmotriti kod progresivne bolesti pluća (7). Budući da je naša bolesnica liječena MTX-om nakon CYC-a, mogući učinci tog lijeka u slučaju naše bolesnice ne mogu se isključiti, iako je bitno napomenuti da je liječenje MTX-om trajalo manje od godinu dana. Nadalje, studije usmjerene na liječenje MTX-om u SSc-u nisu navele pozitivne učinke na zahvaćenost organa (23,24). Međutim, rezultati više studija opisuju povoljne učinke CYC-a na kožne manifestacije kod difuzne kožne SSc. Brojna opservacijska ispitivanja, kao i klinička ispitivanja u kojima se upotrebljavao CYC kao kontrolna

(25–28). Akesson et al. found that patients treated with oral CYC because of pulmonary fibrosis in SSc showed significant improval of skin involvement score after 1 year of treatment (25). Additionally, two studies used CYC as control treatment (while investigating autologous stem cell transplantation as SSc treatment) also showed improvement of skin involvement in the CYC groups (26,27). Furthermore, a recent observational study focused on efficacy of CYC treatment in early diffuse cutaneous SSc, using comparable doses to our case, showed 43% of patients had a clinically relevant response (29). Additionally, the aforementioned effects of CYC where confirmed by a double-blind, randomized, placebo-controlled clinical trial investigating CYC treatment in SSc lung disease, which showed a significant beneficial effect on skin thickening after one year of therapy, with a follow up study showing beneficial effects up to one year after treatment completion (10,30). This corresponds with the case of our patient, where beneficial effects on skin involvement were observed even after the one-year mark with absence of significant organ involvement. . In patients with diffuse SSc, severe organ involvement (namely lung, heart and kidney abnormalities) most commonly occurs in the first 5 years of the disease; if they do not, there is decreased likelihood of it occurring later in the disease (31). Therefore, in the case of our patient, a favorable long-term outcome is to be expected in the future. Although numerous studies have been done, treatment of SSc still remains a challenge for clinicians, as clear treatment guidelines with high evidence levels are lacking, and multiple promising new modalities of treatment are still in different trial phases (32). Nevertheless, as this case demonstrates, CYC should still be considered as an effective first-line treatment in diffuse cutaneous SSc.

CONCLUSION

This case report and literature review has demonstrated that cyclophosphamide can be an effective and safe first-line treatment option for progressive, diffuse cutaneous systemic sclerosis. The efficacy of cyclophosphamide may potentially even extend through multiple years, as, in the case of our patient, there have been no signs of disease progression or severe organ involvement following treatment. Systemic sclerosis remains a diagnostic and treatment challenge which is why further, more extensive clinical trials are needed in order to consolidate treatment guidelines and improve patient outcomes.

Funding: For this work authors did not receive any funding.

Conflict of interest statement: The authors declare no conflict of interest.

metoda liječenja, pokazala su učinkovitost CYC-a na zahvaćenost kože (25–28). Akesson i suradnici otkrili su da su bolesnici liječeni CYC-om koji se primjenjivao oralno zbog plućne fibroze u SSc-u pokazali značajno poboljšanje rezultata zahvaćenosti kože nakon jedne godine liječenja (25). Osim toga, dvije studije u kojima se upotrebljavao CYC kao kontrolna metoda liječenja (tijekom ispitivanja autologne transplantacije matičnih stanica kao metode liječenja SSc-a) također su pokazale poboljšanje zahvaćenosti kože u skupinama liječenim CYC-om (26,27). Nadalje, nedavno provedeno opservacijsko ispitivanje usmjereno na učinkovitost liječenja CYC-om u ranoj difuznoj kožnoj SSc, uz primjenu doza usporedivih s prikazom slučaja naše bolesnice, pokazalo je da je 43% bolesnika imalo klinički relevantan odgovor na tu metodu liječenja (29). Uz to, prethodno spomenuti učinci CYC-a potvrđeni su dvostruko slijepim, randomiziranim kliničkim ispitivanjem kontroliranim placebom u kojem se istraživalo liječenje CYC-om kod plućne bolesti u sistemskoj sklerozi (SSc), koje je pokazalo značajan povoljan učinak na zadebljanje kože nakon jedne godine liječenja, uz naknadno ispitivanje koje je pokazalo povoljne učinke do godinu dana nakon završetka liječenja (10,30). To odgovara slučaju naše bolesnice, kod koje su primijećeni korisni učinci na zahvaćenost kože čak i nakon godinu dana bez značajnog zahvaćanja organa. U bolesnika s difuznom SSc, teška zahvaćenost organa (tj. abnormalnosti pluća, srca i bubrega) najčešće se javlja u prvih pet godina bolesti, a ako do nje ne dođe mala je vjerojatnost da će se pojaviti kasnije u tijeku bolesti (31). Stoga se u slučaju naše bolesnice u budućnosti može očekivati povoljan dugoročni ishod. Iako su provedene brojne studije, liječenje SS-a i dalje ostaje izazov za kliničare jer nedostaju jasne smjernice za liječenje s visokom razinom dokaza, a velik broj novih modaliteta liječenja još uvijek je u različitim fazama ispitivanja (32). Usprkos tomu, kao što ovaj slučaj pokazuje, CYC bi se i dalje trebao smatrati učinkovitim lijekom prve linije liječenja difuzne kožne SSc.

ZAKLJUČAK

Ovaj prikaz bolesnice i pregled literature pokazali su da ciklofosfamid može biti učinkovita i sigurna opcija prve linije liječenja progresivne, difuzne kožne sistemske skleroze. Učinkovitost ciklofosfamida potencijalno se može produljiti i kroz više godina, budući da u slučaju naše bolesnice nije bilo znakova progresije bolesti ili težeg zahvaćanja organa nakon liječenja. Sistemska skleroza ostaje izazov za dijagnostiku i liječenje, zbog čega su potrebna daljnja, opsežnija klinička ispitivanja kako bi se uredile smjernice za liječenje i poboljšali ishodi liječenja bolesnika.

Financiranje: Autori za ovaj rad nisu primili nikakva sredstva.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

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