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BRIEF PAPER KRATKO PRIOPĆENJE

ATYPICAL PRESENTATION OF ANTISYNTHETASE SYNDROME – CASE REPORT

ATIPIČNA PREZENTACIJA ANTISINTETAZNOG SINDROMA – PRIKAZ BOLESNIKA

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Abstract

Anti-synthetase syndrome is an autoimmune disease characterized by myositis and interstitial lung disease. In this paper we report on a middle-aged male patient with an uncommon anti-synthetase syndrome, presenting with pulmonary manifestation before myositis. It is important to identify these patients, because early diagnosis and appropriate treatment are essential for optimal care.

Keywords: Autoimmune diseases – immunology; Myositis – diagnosis, immunology; Lung disease, interstitial – diagnosis, immunology; Autoantibodies – blood; Amino acyl – TRNA synthetase – immunology; Histidine – TRNA ligase – immunology; Glucocorticoids – therapeutic use; Immunosuppressive agents – therapeutic use

Sažetak

Antisintetazni sindrom autoimunosna je bolest koju karakteriziraju miozitis i intersticijska plućna bolest. U ovom radu prikazujemo sredovječnog pacijenta sa sindromom antisintetaze koji se, neuobičajeno, manifestirao plućnim promjenama prije miozitisa. Važno je da takvi bolesnici budu identificirani, jer su rana dijagnoza i odgovarajuće liječenje nužni radi optimalne skrbi za njih.

Ključne riječi: Autoimunosne bolesti – imunologija; Miozitis – dijagnoza, imunologija; Intersticijska plućna bolest – dijagnoza, imunologija; Autoantitijela – u krvi; Aminoacil transportna RNK sintetaza – imunologija; Histidin transportna RNK ligaza – imunologija; Glukokortikoidi – terapijska uporaba; Imunosupresivi – terapijska uporaba

INTRODUCTION

Antisynthetase syndrome (ASS) is a systemic autoimmune syndrome characterized by the presence of autoantibodies to aminoacyl-transfer RNA (tRNA) synthetases (antisynthetase antibodies) (1). Antibodies to anti-histidil (anti-Jo-1) antibodies are the most commonly detected antisynthetase autoantibodies (2). The clinical presentation typically includes: constitu-

UVOD

Antisintetazni sindrom (ASS) skupina je sustavnih autoimunosnih poremećaja koje karakterizira prisutnost protutijela na aminoacil-tRNK sintetazu (antisintetazna protutijela) (1). Najčešća antisintetazna protutijela jesu ona na histidil (anti-Jo1) (2). Tipična klinička slika uključuje miozitis, artralgije ili artritis, Raynaudov fenomen, „mehaničarske ruke" i intersticijsku

tional symptoms, myositis, arthralgias or arthritis, Raynaud phenomenon, mechanic's hands, and interstitial lung disease (ILD). ASS makes up about 30% of inflammatory myopathies (3). The presence of anti-aminoacyl-tRNA synthetase antibodies and *two major* or *one major and two minor criteria are necessary f*or a diagnosis. Major criteria are ILD, polymyositis, or dermatomyositis, while minor criteria are arthritis, Raynaud phenomenon, and mechanic's hands (4). Initial treatment are glucocorticoids, but if necessary, they are combined with immunosuppressive agents such as cyclophosphamide, azathioprine, or mycophenolate mofetil (3).

CASE REPORT

A 45-year-old man presented with a two-month history of general weakness, exhaustion, and chest pain. He had been treated at the Department for Respiratory Diseases under the diagnosis of bilateral pneumonia. The symptoms of general weakness were associated with long-lasting inactivity and bed rest. On discharge, 20-milligram prednisolone tablets once daily were prescribed for further home treatment. At the next follow-up with the pulmonologist one month after discharge from the hospital, an intensification of the previous symptoms with occasional dyspnea was reported. On that occasion, ILD was verified and the chest X-ray showed characteristics of pulmonary fibrosis. Prednisolone was excluded from the therapy. The patient was examined by a rheumatologist who indicated hospitalization for additional diagnostic workup. At the time of hospitalization, pain in the muscles of the pelvis and shoulders occured. The physical examination revealed tachycardia, weak handshake, and difficulty standing up from the squatting position (Gower sign). The initial laboratory workup showed leukocytosis 17x10^9/l (3.4-9.7 10^9/L), as well as elevated aspartate-aminotransferase (AST) 177 U/L (<50U/L), alanine-aminotransferase (ALT) 188U/L (<50U/L), lactate-dehydrogenase (LDH) 548 U/L (<248), creatine kinase (CK) 3184 U/L (0-171 U/L), creatine kinase-MB 112 U/L (0-24 U/L), and C-reactive protein (CRP) 27.2 mg/L (0-5 mg/L). In the urinanalysis total 24-hour urine protein was 0.238 g/24h (<0.15 g/24h). The immunological workup showed negative rheumatoid factor (RF), *anti*-cyclic citrullinated peptide (anti-CCP) antibody, antinuclear antibody (ANA), *anti-double stranded DNA (anti-dsDNA) antibody, anti-ribonuclear protein (RNP) antibody, anti-Smith (Sm) antibody,* and anti-topoisomerase I (anti-Scl-75) antibody, but positive anti-histidil (anti-Jo-1) antibodies, which were 200 (<1 U/l). Spirometry showed a mild restrictive ventilatory disorder, and carbon monoxide diffusing capacity (DLCO) was mildly reduced as well. Serum tumor markers, high-resolution chest CT (HRCT), and ultra-

plućnu bolest (IPB). ASS čini oko 30% upalnih miopatija (3). Dijagnoza se postavlja na temelju prisutnosti protutijela na aminoacil-tRNK sintetazu i dvaju velikih kriterija ili jednoga velikog i dvaju malenih kriterija. Veliki kriteriji jesu IPB, polimiozitis ili dermatomiozitis, a u malene se kriterije ubrajaju artritis, Raynaudov fenomen i „mehaničarske ruke" (4). Osnovnu terapiju ASS-a čine glukokortikoidi, ali oni se, prema potrebi, mogu kombinirati s imunosupresivima kao što su ciklofosfamid, azatioprin ili mikofenolat mofetil (3).

PRIKAZ BOLESNIKA

Naš je pacijent bio 45-godišnji muškarac s dvomjesečnom anamnezom opće slabosti, iscrpljenosti i boli u prsima. Liječen je na Odjelu pulmologije pod dijagnozom bilateralne pneumonije. Simptomi opće slabosti shvaćeni su kao posljedica dugotrajne neaktivnosti i ležanja u krevetu. Otpušten je iz bolnice uz preporuku uzimanja prednizona u dozi od 20 mg na dan. Pri sljedećem pregledu pulmologa, mjesec dana nakon otpusta iz bolnice, primijećeno je intenziviranje prijašnjih simptoma s povremenom dispnejom. Na ovom je pregledu utvrđen IPB, a na RDG-u prsnog koša opisana je plućna fibroza. Prednizon je isključen iz terapije.

Bolesnika je zatim pregledao reumatolog koji je indicirao hospitalnu obradu. Tijekom hospitalizacije javila se bol u mišićima zdjelice i ramena. Fizikalnim pregledom otkriveni su tahikardija, oslabljen stisak šake i teškoće pri ustajanju iz čučnja (Gowersov znak). Inicijalna laboratorijska obrada pokazala je leukocitozu 17 × 10^9/L (3,4 – 9,7 × 10^9/L), kao i povišene vrijednosti aspartat-aminotransferaze (AST) 177 U/L (< 50 U/L), alanin-aminotransferaze (ALT) 188 U/L (< 50 U/L), laktat-dehidrogenaze (LDH) 548 U/L (< 248), kreatin kinaze (CK) 3184 U/L (0 – 171 U/L), kreatin kinaze-MB 112 U/L (0 – 24 U/L) i C-reaktivnog proteina (CRP) 27,2 mg/L (0 – 5 mg/L). Ukupni proteini u 24-satnom urinu iznosili su 0,238 g/24 h (< 0,15 g/24 h). Imunološka obrada pokazala je negativan reumatski faktor (RF). Protutijela na ciklički citrulinski peptid (anti-CCP), antinuklearna protutijela (ANA), protutijela na dvolančani DNK (anti-dsDNK), protutijela na ribonuklearni protein (anti-RNP), anti-Smith protutijela (anti-Sm) i protutijela na topoizomerazu I (anti-Scl 75) bila su negativna, ali su otkrivena pozitivna protutijela na histidil (anti-Jo1), čija je razina bila 200 U/L (< 1 U/L). Spirometrija je pokazala blagi restriktivni poremećaj ventilacije, a difuzijski kapacitet za CO (DLCO) također je bio blago smanjen. Nalazi serumskih tumorskih markera, visokorezolucijskog CT-a toraksa (HRCT) te ultrazvuka srca i mišićno-koštanog sustava bili su normalni. Elektromioneurografija je pokazala malen postotak niskonaponskih polifaznih akcijskih potencijala.

sound of the heart and musculoskeletal system were normal. Electromyoneurography showed a small percentage of low-voltage polyphasic action potentials.

The patient was treated with high doses of corticosteroids, methylprednisolone 1 mg/kg/day, and methotrexate tbl a 15 mg once a week. An improvement was observed in the clinical and laboratory parameters. The corticosteroid dose was gradually reduced and switched to oral prednisolone 60 mg per day, divided in two doses (30 mg + 30 mg). On the last follow-up, six months after hospitalization, the laboratory findings were: CK 66, CK-MB 10.7, AST 14, and ALT 18. The other parameters were within the reference limits, and the prednisolone dose was reduced to 15 mg daily with the same metothrexate dose.

DISCUSSION

ASS is a rare systemic autoimmune disease that affects multiple organs. The prevalence is 1.5 per 100,000 population. The mean age at diagnosis is 50 years, with a predominance in females (2 : 1) (5). Myositis, ILD, and polyarthritis followed by fever and skin involvement are the classic clinical manifestations of ASS (6). The hallmark of the disease are antibodies against aminoacyl-tRNA synthetase, most commonly anti-Jo-1 antibodies, in 80% of cases (3). ILD occurs in more than 60% of cases and is the major cause of morbidity (7). Routine testing for ASS antibodies in all patients with ILD without an obvious etiology is important because they have implications regarding the choice of therapy (8). Myositis occurs in 90% of cases, but it is of note that it may not be part of the initial clinical presentation of ASS. In one series of ILD patients with ASS, myositis as an initial symptom was present in only 31% of them. Myositis can occur months and even years after ILD (9). In our case, ILD preceded myositis. A literature review shows that it occurs at a percentage of 10-30%, which is not negligible (10). In our patient, in the initial stages of the disease ILD presented on X ray as fibrosis according to the radiologist's report, but clinically it was more consistent with interstitial pneumonitis, as an early stage of ILD. Because of that, we started treatment with prednisolone, with a favorable response verified by the chest HRCT done after admission to the Rheumatology Department, which was normal. Pulmonary function tests showed a mild restrictive ventilation disorder, supporting the initial findings (FVC 78%; FEV1 73%; DLCO 65%).

Joint involvement occurs in more than 50%, mechanic's hands in 30%, and Raynaud phenomenon in 40% of ASS cases (6).

A similar case report was published by Priyangika et al. In that case the patient initially presented with progressive exertional dyspnea. HRCT was performed, as

Bolesnik je liječen visokim dozama kortikosteroida (metilprednizolon u dozi od 1 mg/kg/dan) i peroralnim metotreksatom u dozi od 15 mg na tjedan, nakon čega dolazi do poboljšanja kliničkih i laboratorijskih parametara. Doza kortikosteroida postupno je snižena i promijenjena iz intravenskoga u peroralni prednizon od 60 mg na dan, podijeljena na dvije doze (30 mg + 30 mg). Pri posljednjoj kontroli, šest mjeseci poslije hospitalizacije, vrijednost CK bila je 66, CK-MB 10,7, AST-a 14, ALT-a 18, uz uredne vrijednosti ostalih mjerenih parametara, a doza prednizona snižena je na 15 mg, uz istu dozu metotreksata.

RASPRAVA

ASS rijetka je sustavna autoimunosna multiorganska bolest. Prevalencija iznosi 1,5 na 100.000 stanovnika. Prosječna dob bolesnika pri dijagnozi jest 50 godina, a češće se javlja u žena (2 : 1) (5). Miozitis, IPB i poliartritis praćeni febrilitetom i afekcijom kože tipična su klinička manifestacija ASS-a (6). Za bolest su karakteristična protutijela na aminoacil-tRNK sintetazu od kojih je najčešće protutijelo na histidil (anti-Jo1) koje se javlja u 80% bolesnika (3). Intersticijska plućna bolest javlja se u više od 60% bolesnika i glavni je uzrok morbiditeta (7). Rutinsko određivanje protutijela na ASS u svih bolesnika s IPB-om nejasne etiologije važno je radi odabira terapije (8). Miozitis se javlja u 90% bolesnika, ali valja naglasiti da ne mora biti jedan od početnih kliničkih simptoma ASS-a. U jednoj seriji bolesnika s IPB-om u ASS-u miozitis je kao početni simptom bio prisutan u njih samo 31%. Miozitis se može javiti mjesecima, pa i godinama poslije pojave IPB-a (9). U našeg je bolesnika IPB prethodio miozitisu. Uvidom u literaturu može se primijetiti da se to događa kod čak 10 – 30% pacijenata, što nije zanemariv postotak (10). Našem je pacijentu u početnoj fazi bolesti čak i na RDG-u pluća opisan IPB u obliku fibroze, kao što je navedeno u radiološkom nalazu, dok je klinički nalaz govorio više u prilog intersticijskom pneumonitisu kao ranoj fazi IPB-a. Zbog toga smo liječenje počeli prednizonom, uz povoljan odgovor, na što je upućivao i uredan nalaz HRCT-a toraksa, učinjenoga nakon prijma na Odjel za reumatologiju. Testovi plućne funkcije pokazali su blag restriktivni poremećaj ventilacije, u skladu s početnim nalazima (FVC 78%; FEV1 73%; DLCO 65%).

Afekcija zglobova javlja se u više od 50% bolesnika s ASS-om, „mehaničarske ruke" u njih 30%, a Raynaudov fenomen u 40% takvih pacijenata (6).

Sličan prikaz bolesnika objavili su Priyangika i suradnici. Njihov se pacijent inicijalno javio zbog progresivne dispneje pri naporu. Učinjeni su HRCT toraksa i transbronhalna biopsija pluća te je postavljena dijagnoza kriptogene organizirane pneumonije. Dvije godine poslije pacijentu su se javile boli u mišićima.

well as transbronchial lung biopsy, and the diagnosis of organizing pneumonia was made. Two years later the patient presented with muscle pain, and the diagnosic workup revealed elevented CK and CRP with positive anti-Jo-1 antibodies, but without arthritis or arthralgias, Raynaud phenomenon, or mechanic's hands. With high-dose prednisolone and azathioprine, the patient's CK and inflammatory markers normalized (11). He had positive anti-Jo-1 antibodies with ILD and muscle involvement, but without Raynaud phenomenon, joint involvement, and mechanics hands, which does not exclude the possibility of their occurrence in the future.

In conclusion, our case shows that in patients with ILD without a known etiology the presence of ASS must be considered. Early diagnosis and the adequate treatment are essential for optimal patient care.

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Dijagnostičkom obradom nađeni su: povišene vrijednosti CK i CRP-a, pozitivna protutijela na histidil (anti-Jo1) bez prisutnosti artritisa ili artralgija, Raynaudov fenomen i „mehaničarske ruke". Uz liječenje visokim dozama prednizona i azatioprina vrijednosti CK i upalnih parametara normalizirale su se (11). Naš je bolesnik bio pozitivan na anti-Jo1, imao je IPB i zahvaćenost mišića, ali bez Raynaudova fenomena, afekcije zglobova i „mehaničarskih ruku", što ne znači da se te manifestacije možda neće pojaviti u budućnosti.

Zaključno, naš prikaz upozorava na to da bi kod bolesnika s idiopatskim IPB-om trebalo razmotriti i ASS kao mogući uzrok. Rano dijagnosticiranje i prikladno liječenje nužni su radi optimalne skrbi za bolesnika.

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REFERENCES / LITERATURA

1. Targoff IN. Autoantibodies and their significance in myositis. Curr Rheumatol Rep. 2008;10(4):333–40.
2. Cojocaru M, Cojocaru IM, Chicos B. New Insights into Antisynthetase Syndrome. Maedica (Buchar). 2016;11(2):130–5.
3. Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase syndrome. Curr Rheumatol Rep. 2011;13(3):175–81.
4. Witt LJ, Curran JJ, Strek ME. The Diagnosis and Treatment of Antisynthetase Syndrome. Clin Pulm Med. 2016;23(5):218–26.
5. Solomon J, Swigris JJ, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. J Bras Pneumol. 2011;37(1):100–9.
6. Chatterjee S, Prayson R, Farver C. Antisynthetase syndrome: not just an inflammatory myopathy. Cleve Clin J Med. 2013; 80(10):655–66.
7. Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatology (Oxford). 2009;48(8):968–71.
8. Aslam F, Russell EB. Fellow's forum case report: diagnosing antisynthetase syndrome. Rheumatologist. 2013;1–6.
9. Tillie-Leblond I, Wislez M, Valeyre D i sur. Interstitial lung disease and anti-Jo-1 antibodies: difference between acute and gradual onset. Thorax. 2008;63:53–9.
10. Labirua-Iturburu A, Selva-O'Callaghan A, Vincze M i sur. Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome: clinical manifestations in a series of patients from a European multicenter study (EUMYONET) and review of the literature. Medicine. 2012;91(4):206–11.
11. Thanuja Nilushi Priyangika SM, Karunarathna WGSG, Liyanage I i sur. Organizing pneumonia as the first manifestation of anti-synthetase syndrome. BMC Res Notes. 2016;9:290.