

CASE PRESENTATION

Rheumatoid arthritis – an enemy of the heart

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Abstract: Rheumatoid arthritis (RA) is a rheumatic inflammatory disease mainly characterized by chronic synovitis of peripheral joints leading to osteoarticular destructions which consequently involves the decrease in the joint function. RA is frequently associated with a high cardio-vascular (CV) risk involved in an increased CV morbidity and mortality of such patients compared with general population. The traditional risk factors for atherosclerosis are more prevalent in RA patients, but they do not completely explain the excess of CV risk. Early and accelerated atherosclerosis in patients with active RA may cause frequent CV events, the common element of these two diseases being chronic inflammation. We present a case of active RA complicated with acute myocardial infarction developed when the patient discontinued the immunosuppressive therapy with conventional synthetic Disease-Modifying AntiRheumatic Drugs (cs DMARDs) treated with inserting a coronary stent; a stent thrombosis appeared because the patient was noncompliant and discontinued the indicated treatment.

Keywords: rheumatoid arthritis, cardiovascular risk, chronic inflammation, Treat-to-Target.

Rezumat: Poliartrita reumatoidă (PR) este o boală reumatică inflamatoare caracterizată în special prin sinovită cronică a articulațiilor periferice ducând la distrucții osteo-articulare care implică consecutiv scăderea funcției articulare. PR este frecvent asociată cu un risc cardiovascular (CV) crescut implicat în creșterea morbidității și mortalității CV ale acestor pacienți comparativ cu populația generală. Factorii de risc tradiționali pentru ateroscleroză sunt mai prevalenți la pacienții cu PR, dar ei nu explică în totalitate excesul de risc CV. Ateroscleroza precoce și accelerată la pacienții cu PR activă poate cauza evenimente CV frecvente, elementul comun al acestor două boli fiind inflamația cronică. Noi prezentăm un caz de PR activă complicată cu infarct miocardic acut dezvoltat când pacienta a întrerupt terapia imunosupresivă cu conventional synthetic Disease-Modifying AntiRheumatic Drugs (cs DMARDs) tratată prin inserția unui stent coronarian; o tromboză a stentului a apărut pentru că pacienta a fost necompliantă și a renunțat la tratamentul indicat.

Cuvinte cheie: poliartrita reumatoidă, risc cardiovascular, inflamație cronică, terapie conform țintei

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic rheumatic inflammatory disease, predominantly affecting peripheral joints with their possible anatomical destruction and reduction of function. It is now well established that RA is associated with increases in morbidity and mortality compared with general population. RA increases CV morbidity and mortality by up to 50% compared with general population and CV disease (CVD) is the leading cause of death in RA^{1,2}.

There is a high risk of acute myocardial infarction (AMI) in patients with RA and this risk is similar with the risk of AMI in diabetes mellitus and it generally corresponds with the risk of AMI in non-RA subjects 10 years older³. There is a nationwide retrospective cohort study which indicates that AMI risk increased by 38% in RA patients compared to the general popu-

lation and the presence of comorbidities increased the AMI risk independently⁴.

Early and accelerated atherosclerosis is considered to be responsible for the more frequent CV events in RA patients. Traditional risk factors for atherosclerosis do not entirely explain the high risk of CV events in patients with RA. Chronic inflammation is a common feature of both RA and atherosclerosis due to many similarities between RA and atherosclerosis. The pathologic processes in both RA and atherosclerosis are similar, if not common, being immune mediated by Th1 and Th17⁵. Common inflammatory mediators such as tumor necrosis factor (TNF), Receptor activator of NF- κ B ligand (RANKL)/Receptor activator of NF- κ B (RANK)/osteoprotegerin (OPG) system, CD40/CD40 ligand orchestrate pathophysiological processes in RA and atherosclerosis⁶.

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Growing evidence suggests that this excessive inflammatory burden is accountable for the “lipid paradox” in RA, in which cholesterol-an important CV risk factor in the general population-is inversely related to CV risk in patients with untreated RA. In contrast, suppression of RA-associated inflammation coincides with some increases in lipid values, but also a reduction in CV events⁷.

As the CV risk in RA patients is high especially in active disease a strict monitoring of patient in view of a correct treatment to reduce disease activity is mandatory in clinical practice.

There is also known that treatment with statins decreases the risk of AMI not only in general population, but also in RA patients. A population-based cohort study showed that RA patients who discontinue statins have increased risk of AMI⁸.

There is a different pattern of the CVD in RA compared with general population characterized by a greater risk for patients to develop heart failure or sudden death. No differences were found regarding the number of acute coronary lesions or the degree of stenosis in patients with RA and AMI, but different histological characteristics of atherosclerotic plaques were described; the plaques tend to have a greater degree of inflammation and instability making them more prone to rupture and consecutive thrombosis⁹.

It is also known that many scores are used to evaluate CV risk in general population, but a complete score which takes into account both traditional risk factors for atherosclerosis and specific factors for RA is still expected being necessary in clinical practice.

CASE REPORT

We present the case of a 64 year old female, ex-smoker, having no family history of cardiovascular or rheumatic diseases who is currently admitted to “Sf. Maria” Clinical Hospital for clinical and biological reassessment of her underlying disease - seropositive RA.

The symptoms of the patient started in June 1999 when she accused painful swelling of both knees and ankles. The symptoms at that time were interpreted as the onset of spondylarthritis as the patient was tested positive for the presence of HLA-B27 antigen. She was given immunosuppressive treatment with sulfasalazine (3 g/day) and nonsteroidal anti-inflammatory drugs (NSAIDs).

In January 2000 she was admitted for the first time to “Sf. Maria” Clinical Hospital with the same arthralgias but also with swelling and inflammatory pain in her metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of both hands. She also had high levels of the inflammatory tests (ESR, C reactive protein, fibrinogen) and high titer of rheumatoid factor (RF). Given these findings she was then diagnosed with seropositive RA and the treatment was initiated with methotrexate (5 mg/week) plus sulfasalazine (1 g/day) and prednisone (20 mg/day).

Between 2000 and 2007, the patient’s disease took various aspects requiring small changes in the corticosteroid dosage or the sulfasalazine dosage based on the fact that sulfasalazine is the choice immunosuppressive for peripheral articular inflammatory symptoms and the patient’s major pain was in her right knee.

In July 2012, after more than 10 years of evolution of rheumatic disease, the patient was diagnosed with coronary artery disease after she experienced an episode of cardiac-type chest pain which brought her to the emergency room of a country hospital. A possible myocardial infarction was eliminated from the differential diagnosis at that time because the ECG showed no signs of coronary acute obstruction and myocardial enzymes were negative.

In July 2013 (one year later), the patient stopped taking any kind of immunosuppressive medication out of personal reasons; she only took NSAIDs such as Diclofenac (150 mg/day) during periods of severe joint pain.

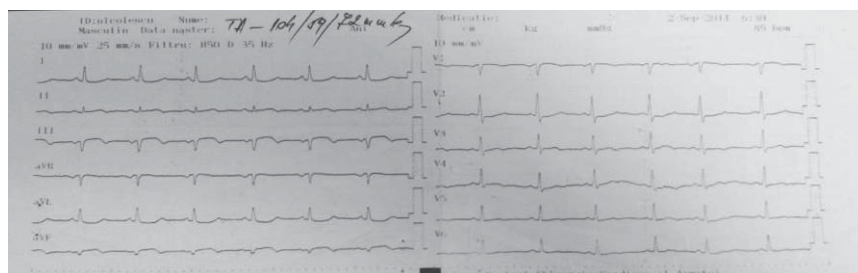


Figure 1. ECG tracing from 2014 (one and a half week after the myocardial infarction) – Q waves in DIII, aVF, ST elevation in DII, DIII, aVF and negative T waves in DII, DIII, aVF.



Figure 2. Radiocubito carpian (RCC) joint swelling and atrophy of the interosseus muscles.

All this led to the main CV event that happened in August 2014, an infero-lateral AMI which was rapidly treated by primary percutaneous transluminal coronary angioplasty (PTCA) and a drug-eluting stent (DES) was embedded at the thrombosis site on the right coronary artery.

Unfortunately, the patient is uncompliant to the double antiplatelet therapy (both clopidogrel and as-



Figure 3. Swelling of the bilateral knees (right>left) with valgus deformity.



Figure 4. Permanent proximal interphalangean (PIP) flexion in 2nd and 3rd fingers of bothfeet; right hallux valgus.

pirine), therefore two weeks after the CV event she suffers a new one, thrombosis in the newly implanted DES stent, also being quickly treated by balloon angioplasty with the restoration of a satisfactory coronary blood flow TIMI 3. After 3 weeks the patient's rheumatic disease was reassessed at "Sf. Maria" Clinical Hospital and, as expected at this moment, the Disease Activity Score 28 (DAS28) indicated a highly active disease (DAS28=5.3). Immunosuppressive therapy was restarted with methotrexate (20 mg/week).

The subsequent check-ups revealed a similar clinical picture: inflammatory arthralgias mostly of the radiocubito carpal (RCC) and metacarpophalangeal (MCP) left joints with synovitis demonstrated by musculoskeletal ultrasound, but the markers of inflammation (ESR, C reactive protein and fibrinogen) were within normal range.

Remission of the disease for early RA and low disease activity for established RA represents the goal of treatment in accordance with Treat-to-Target strategy. For our patient who has an established form of the disease, targeting the low disease activity represents the target of the therapy. The absence of biological inflammatory syndrome made it impossible to prescribe biological treatment in accordance with National Protocol for Biological Therapies in RA, therefore a triple immunosuppressive therapy was given (methotrexate plus sulfasalazine plus hydroxychloroquine) as the last resort; she became intolerant to sulfasalazine and hydroxychloroquine proved to be inefficient in her case, so she is currently on methotrexate (20 mg/week) and prednisone (10 mg prednisone) alongside her conventional CV treatment which consists of double antiplatelet therapy, a beta blocker and a statin; her evolution has been uneventful ever since.

DISCUSSION

We felt the need to present this clinical case of a female patient diagnosed with RA who developed an AMI ten years after the positive diagnosis at a time when she discontinued immunosuppressive treatment taking only diclofenac (150 mg/day) well known for its CV adverse effects. We consider it a very complex because the solution of the AMI in this female patient with longstanding, active form of RA was PCTA complicated with thrombosis of the stent, also because of her own decision to interrupt the indicated treatment.

Our case confirms once again the data in literature regarding the increased CV risk in patients with RA as well as high incidence of AMI, especially in patients with active RA. The significance of this problem drew

European League Against Rheumatism (EULAR) attention which published in 2009 and 2016 two sets of recommendations CV risk management in patients with RA and other forms of inflammatory disease. Unlike to 2009 recommendations¹⁰ which multiply by 1.5 the CV risk in patients with RA having special features such as extraarticular manifestations, high levels of Rheumatoid Factor (RF) and anti-Cyclic Citrullinated Peptide (CCP) antibodies and a longer than 10 years evolution, the 2016 recommendations¹¹ reconsider this situation, mentioning that these RA specific features should no longer be considered necessary for the application of that multiplication factor as there is a CV risk even in patients in the early stages of the disease without extraarticular manifestations.

Within this context our case report underlines once again the CV risk in RA patients and more than that stresses that factors involved in this CV risk such as activity of the disease, improper medication and uncompliances to treatment are very important in this setting as our title suggests: RA-an enemy of the heart.

In the case of our patient the fact that the target of low disease activity had not been reached she experienced an AMI after giving up treatment during the high activity of the disease.

Besides the high activity of the disease other contributing factors leading to AMI include the treatment with diclofenac known for its CV risk and the fact that she was noncompliant to her doctor's advice and she stopped immunosuppressive treatment before reaching the target.

The presented clinical case reveals a RA patient who suffered an AMI fifteen years after she was diagnosed with RA. The CV event happened during an active phase of the disease (DAS28=5.3) and when no immunosuppressive therapy was present.

The treatment of RA in accordance with the principle of "Treat to Target" is very important in decreasing the CV risk in patients with active form of the disease. In the context of the treatment, Methotrexate (MTX), considered a mainstay of therapy for RA, can ameliorate some of this excess CV risk, an effect that has not been seen consistently with other disease-modifying antirheumatic drugs (DMARDs). The cardioprotective action of MTX may occur through reducing systemic inflammation and by directly affecting some of the cellular mechanisms that lead to atherosclerosis. There are several effects of MTX in CV disease: MTX reduce all-cause CV disease, heart failure (strong strength of effect), AMI and stroke (moderate strength of effect). It is very important to add that

MTX increase hyperhomocysteinaemia, but this effect is ameliorated by folic acid supplementation (strong strength of effect)^{12,13}.

A study designed to explore the effect of disease modifying anti-rheumatic drugs (DMARDs) on synovial inflammation as well as on atherosclerotic indices in patients with early rheumatoid arthritis shows that after 1 year of treatment there is a significant improvement of variables like erythrocyte sedimentation rate (ESR) and high sensitivity C-reactive protein (hsCRP), DAS28, HAQ-DI and a significant decrease carotid intima-media thickness (cIMT) from the baseline¹⁴.

In the treatment of the RA, NSAIDs represent another very important medication used to decrease the signs and symptoms of the inflammation, but unfortunately they are associated with a high risk of CV diseases: arterial hypertension, ischaemic heart disease, heart failure. In order to best choice of a NSAID in patients with RA is very important to take into consideration not only the type of the drug (COX-1, COX-2), but also the profile of the patient with this rheumatic disease. If NSAIDs use is unavoidable, blood pressure must be checked regularly and in this situation naproxen is probably the first choice. Furthermore, the combination of NSAIDs and aspirin is not advisable, since NSAIDs may impair the antiplatelet function of aspirin¹⁵.

At the same time, the glucocorticosteroids are very powerful anti-inflammatory drugs and are commonly used as treatment for patients with RA. They have strong anti-inflammatory properties which could mean that GCs have anti-atherosclerotic effects. However, in the general population, therapeutic doses of oral GCs (≥ 7.5 mg/day) have been associated with increased CV disease and all-cause mortality. The effect of GCs on the CV risk probably depends on several factors, such as the population of RA patients, the circumstances and way it is used, the dosage and treatment duration¹⁶.

For all reasons stated before, it is important to have tools that help in assessing the CV risk in patients with RA. Though it may seem that in medical literature exist more than one score that can predict one's CV risk (for instance: SCORE, Framingham BMI, Framingham lipids, etc), it is also true that these scores take into consideration only traditional risk factors like hypertension, diabetes, smoking, cholesterol level, etc. In 2008 in BMJ was published an article about the development of a new CV risk score named QRISK2 which has proven to be most complete one until now and the one which considers RA among the CV risk

factors. The results of the calibration and discrimination statistics for QRISK2 were significantly better than those for the modified Framingham score in the validation sample. At the 10 year risk threshold of 20%, the population identified by QRISK2 was at higher risk of a CV event than the population identified by the modified algorithm¹⁷.

There are several studies showing the pleiotropic effect of statins as adjunctive therapy to specific treatment in patients with RA. A double-blinded, randomized placebo-controlled trial that included 116 patients with RA randomised to receive 40 mg atorvastatin or placebo in association with DMARDs showed that after 6 months of treatment there was a significant improvement of DAS28 on atorvastatin group compared to placebo and a decrease of CRP and ESR by 50% and 28%, respectively in treated group compared to placebo¹⁸.

The implication of our case for the time being lies in the fact that close monitoring of the RA and the correct treatment not only of the rheumatic disease but also of the CV disease represents a proper solution of the case leading to survival and even to a good quality of life.

We consider that further presentations of similar cases and longer studies on case series and clinical studies on population in Romania will be beneficial for rheumatologists and cardiologists.

CONCLUSIONS

1. There is an increased risk for developing coronary artery disease secondary to early and accelerated atherosclerosis in RA patients as demonstrated once again by the case of our patient.
2. A strict therapeutic monitoring of this patient should be made in accordance with “Treat-to-Target” strategy in order to obtain sustained low disease activity.
3. Of all the CV risk scores, QRISK2 which also includes RA as a CV risk factor, seems to be the most proper.
4. A collaboration between rheumatologists and cardiologists has proved important for improving the patients condition in saving her life.
5. Our case report is in agreement with published medical literature and other similar cases should be further made known to clinicians for a better management of the patients.

Conflict of interest: none declared.

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