

Complete Atrioventricular (AV) Block as a Cardiac Complication of Rheumatoid Arthritis: A Rare Case Report

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ABSTRACT

Atrioventricular block (AVB) is a rare complication of rheumatoid arthritis (RA). Complete AVB in people with RA significantly increases cardiovascular morbidity and doubles the mortality risk. We report on a 48-year-old woman presenting with dyspnea and peripheral edema, with symptoms of polyarthritis for 3 years. Physical findings included bradycardia, bilateral rales, and finger deformities consistent with RA. Electrocardiography featured complete AVB, and a thoracic computed tomography scan showed a mosaic appearance with fibrosis, bronchiectasis, and partial atelectasis of the lungs. Further tests showed elevated levels of C-reactive protein, rheumatoid factor, and several inflammatory cytokines. Transient followed by permanent pacemaker placement was performed along with pharmacological treatments, including intravenous (IV) methylprednisolone pulse therapy and IV tocilizumab. Cardiac involvement in RA usually takes the form of pericardial effusion, heart failure, myocarditis, and coronary artery disease. Complete AVB is a rare but important extra-articular involvement in RA that warrants early recognition and treatment with a pacemaker, anti-inflammatory drugs, and disease-modifying antirheumatic drugs.

Keywords: cardiac complication, complete atrioventricular (AV) block, rheumatoid arthritis,

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, immune-mediated disease that targets primarily the joints and has extra-articular manifestations that can affect various organs, such as the bone, the lungs, and the heart.¹⁻³ RA is a major health issue worldwide. For example, about 18 million individuals globally were afflicted by RA in 2019, and the prevalence was around 209 cases per 100,000 population in 2020.^{4,5} With a global prevalence rate of RA of 0.5–1% and Indonesia's population of 268 million in 2020, it is estimated that there are at least 1.3 million people affected by RA in Indonesia.⁶ A recent study showed a remission

rate of 24.5% and low disease activity in 18.5% among Indonesian patients with RA, which suggests that RA continues to be a high-burden disease for these patients.⁷ RA can lead to substantial disability and early mortality: about 60% of RA patients are unable to work, and the average life expectancy is reduced by 7 years for men and 3 years for women compared with the general population.⁶

Cardiac involvement in RA can include pericardial effusion, cardiomyopathy, valvular disease, coronary artery disease (CAD), and conduction defects. Atrioventricular (AV) block (AVB) is a rare complication of RA that is usually complete and occurs in 0.1% of RA patients.

Milder degrees of block may precede the onset of complete AVB, occasionally with intervals of normal conduction in between.⁸⁻¹⁰ The occurrence of complete AVB in RA can impact the vital prognosis because RA significantly increases cardiovascular morbidity and doubles the mortality risk; for example, cardiovascular events contribute to about 50% of premature deaths in people with RA.¹

Vigilant cardiac monitoring and collaborative management are needed to prevent the potentially severe cardiac complications in RA patients. We present a case of a 48-year-old woman diagnosed with RA with cardiac manifestation of a complete AVB.

CASE ILLUSTRATION

A 48-year-old woman was admitted to the emergency room with dyspnea that had started 2 days before admission. One week before admission, the patient experienced fatigue but no fever or chest pain. She sought medical care 3 days before from an alternative medicine practitioner and was administered around 1700 mL of intravenous (IV) fluids and discharged. The patient experienced dyspnea and swollen legs the day after, and she went to the emergency room. The patient had experienced pain, stiffness, and intermittent swelling of the fingers of both hands, shoulders, and sometimes knees for 3 years preceding her admission. The pain was felt during movement in any direction, and her joint stiffness lasted longer than 30 minutes upon waking in the morning. The pain and stiffness worsened 1 month before admission, and her left index finger seemed enlarged.

The patient had no history of hypertension, diabetes, asthma, allergies, or previous diagnosis of autoimmune disorders. The initial physical findings included regular bradycardia of 46 bpm, peripheral oxygen saturation of 98% at 4 L/min via a nasal cannula, coarse rales in both lungs, slight pretibial pitting edema, boutonniere deformity of the left thumb, swan neck deformity of the third digit of the left hand, and ulnar deviation in both hands. A chest X-ray revealed cardiomegaly with increased pulmonary markings, cephalization, peribronchial cuffing with perihilar haze, and multiple Kerley A and

Kerley B lines consistent with pulmonary edema. Bilateral X-ray of the hands showed narrowed joint spaces of the radiocarpal, ulnocarpal, and intercarpal joints with subarticular sclerosis, as well as marginal erosion of the carpal bones consistent with RA with bilateral scaphoid bone rotation, indicative of carpal instability. Electrocardiography (ECG) demonstrated complete AVB with no signs of ischemia or infarction (**Figure 1**). Laboratory results showed elevated levels of quantitative troponin I (19.4 ng/mL), C-reactive protein (51.6 mg/dL), and ferritin (262.91 ng/mL). The comprehensive metabolic panel, procalcitonin level, and thyroid function test were within the normal range.

The patient was initially assessed as having cardiogenic pulmonary edema, symptomatic bradycardia caused by complete AVB, and severe RA. She was initially treated with atropine sulfate and subsequently with a dopamine IV drip. However, the rhythm did not convert, a temporary pacemaker (TPM) was inserted, and the patient was admitted to the intensive cardiovascular care unit. Echocardiography showed non-dilated heart chambers, concentric left ventricle (LV) hypertrophy, normal LV systolic function (ejection fraction 57%), grade 1 LV diastolic dysfunction, small pericardial effusion, and a visible TPM in the right atrium and ventricle.

Further laboratory tests were performed. The patient had elevated levels of total cholesterol (324 mg/dL) and LDL (246 mg/dL). Further tests showed an elevated rheumatoid factor level of 284.0 U/mL but normal anti-ds-DNA, C3, and C4 levels, a negative ANA profile test, and antiphospholipid antibodies. Laboratory results showed elevated cytokine levels: interleukin 10 (IL-10), 67.36 pg/mL; TNF- α , 506.50 pg/mL; and IFN- γ , 82.45 pg/mL. The IL-6 level was normal (5.15 pg/mL). A thoracic lung computed tomography (CT) scan with volumetry showed cardiomegaly with atherosclerosis of the ascending aorta and aortic arch, and a mosaic appearance in both lungs showing fibrosis, bronchiectasis, and partial atelectasis of segments 1/2, 3, and 5 of the left lung (**Figure 2**).

The patient was diagnosed with RA, with the cardiac involvement of autoimmune

cardiomyopathy and complete AVB, lung involvement of interstitial lung disease (ILD), and dyslipidemia. The patient was treated with IV methylprednisolone 500 mg per day for 3 days, gradually tapered down, atorvastatin 40 mg qd, furosemide 40 mg qd, calcium carbonate 500 mg bid, and vitamin D 1000 IU qd. A permanent pacemaker (PPM) was placed 10 days later. The patient showed clinical improvement in the dyspnea a few days after PPM placement and was stepped down to a regular ward. Cardiac magnetic resonance (CMR) imaging with contrast later showed a global normokinetic LV with normal morphological and systolic function and no edema, fibrosis, or pericardial effusion. After discussion with the rheumatology team, IV

tocilizumab at a dose of 480 mg every 4 weeks was initiated after prior negative screenings of active or latent infections. The patient was discharged with no dyspnea, chest pain, or arthralgia. Follow-up visits and subsequent doses of tocilizumab were planned.

DISCUSSION

Cardiovascular disease is the leading cause of death globally and has an incidence of 30–60% in RA patients. Cardiac involvement in RA is commonly in the form of pericardial effusion, heart failure, myocarditis, and CAD.¹¹ Conduction disorders are more common than arrhythmias in patients with RA, but occur more often in the form of a right bundle branch

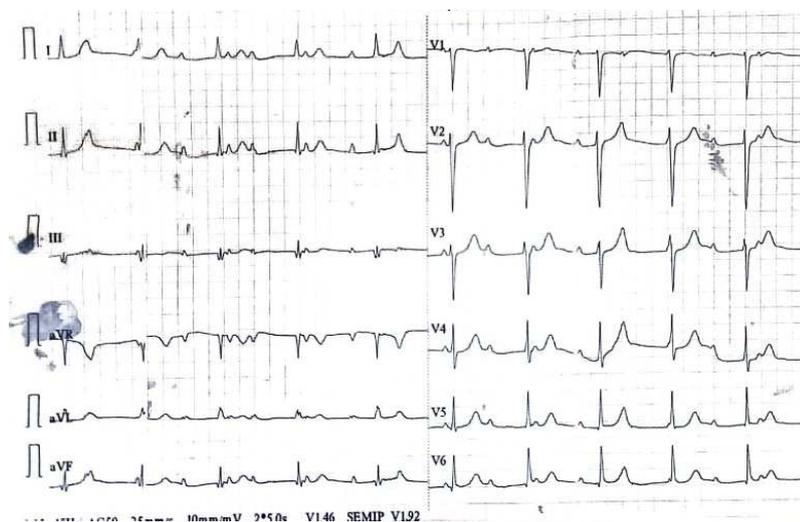


Figure 1. Electrocardiogram showing complete AVB.

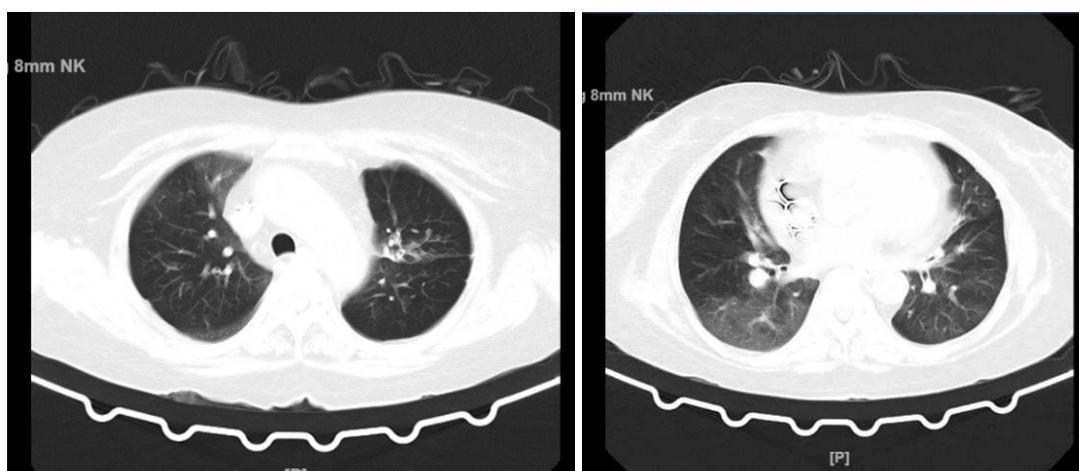


Figure 2. Thoracic CT scan showing mosaic appearance of both lungs with fibrosis, bronchiectasis, and partial atelectasis of the lungs.

block.¹² Complete AVB in RA patients occurs at an average age of 60.2 years (range 36–79 years) at a female-to-male ratio of 19:9 and a mean prior duration of RA of 12 years (range 2.2–49 years). This complication usually has a sudden onset and remains permanent. AVB in RA patients is often discovered after a syncope or occurs sporadically and does not respond to anti-inflammatory treatment or disease-modifying antirheumatic drugs (DMARDs).⁹

Primary infiltration of conducting tissue, such as the AV node, either by mononuclear cells or a rheumatoid granuloma, is thought to cause conduction disorders in RA patients. Various other mechanisms thought to contribute include CAD caused by accelerated atherosclerosis, nonspecific inflammatory lesions, hemorrhage into rheumatoid nodules, or extension of inflammatory lesions from the mitral or aortic valve, amyloid deposition, or vasculitis of the arteries supplying conductive tissues.^{13–15} Conduction disorders can be diagnosed by a simple ECG. CMR can be helpful in the early diagnosis of cardiac involvement in RA, including in asymptomatic patients. CMR can be used to identify signs of numerous structural or functional abnormalities, such as early LV dysfunction, acceleration of atherosclerosis, and pulmonary hypertension with right ventricular function measurements.^{16,17}

This patient had newly diagnosed RA with pathognomonic articular signs and extra-articular involvement of the heart in the form of complete AVB, pericardial effusion, and cardiomyopathy, as well as the lungs in the form of ILD. As in earlier reports, the patient fit the demographic characteristics of a woman who experienced the sudden onset of AVB. Complete AVB in RA is usually permanent and does not respond to corticosteroids or DMARDs.^{8,9} Thus, PPM placement was performed.

The cytokine IL-6 plays an important role in RA pathogenesis, including the extra-articular manifestations, and its level correlates with disease activity and radiological joint progression.¹⁸ IL-6 promotes proinflammatory activity, stimulates acute phase proteins, induces autoantibody production, and has other known actions.^{19,20} IL-6 also has a central role in

cardiovascular involvement; for example, IL-6 elevation may be associated with atherosclerosis, endothelial cell activation, and prothrombotic effects, and can promote the proliferation of vascular smooth muscle cells and an increase in macrophage lipid content.²¹ IL-6 is also associated with AVB. In vivo animal studies have shown that elevated IL-6 levels are associated with downregulation of connexin 43 and that reduced connexin 43 levels lead to electrical remodeling of the AV node, which causes AV conduction delay and subsequent AVB.²²

Tocilizumab inhibits IL-6 receptors and is an established treatment for RA.^{23–25} Tocilizumab significantly improves patient-reported outcomes and health-related quality of life in RA patients with systemic symptoms and extra-articular involvement, including those with moderate-to-severe disease activity, including patients with an inadequate response to conventional synthetic DMARDs and TNF inhibitors, and has a reassuring safety profile.^{24,25} Despite the previous concerns and the increase in blood cholesterol level, tocilizumab may benefit the management of RA-related cardiovascular risk because of its inhibition of inflammation-induced atherogenesis and the complications of type 2 diabetes mellitus (T2DM) by decreasing insulin resistance and inhibiting inflammasomes.^{26–29} Tocilizumab may also have antiarrhythmic potential by reducing QTc prolongation in RA patients.³⁰

Although robust clinical trials are unavailable, IL-6 inhibition may be a useful anti-arrhythmic approach for treating inflammation-induced AVB.²² There are no established predictors of the response to tocilizumab treatment, and the role of serum IL-6 and acute-phase reactants remains controversial.^{31,32} Even though the TNF α level was elevated (506.50 pg/mL) in this patient, TNF α inhibitors are associated with the risk of adverse cardiovascular events, including worsening of heart failure.^{33,34} Moreover, case reports have noted the occurrence of AVB after infliximab infusion.^{35,36} Tocilizumab is also used to treat RA-associated ILD. A previous study of tocilizumab treatment in 28 patients with RA-associated ILD reported stable results in pulmonary function tests in 56% of patients

and high-resolution CT scans in 89.3%.³⁷ After discussing this patient with the rheumatology team, IV tocilizumab was initiated together with methylprednisolone. Despite the normal IL-6 levels, the patient's condition improved significantly, and she was discharged with no further symptoms.

CONCLUSION

Cardiovascular complications are the main cause of death in patients with RA. Complete AVB is a rare extra-articular involvement in RA that is usually permanent and can lead to increased mortality. Early recognition and treatment with a pacemaker are important for reducing morbidity and mortality in RA patients.

CONFLICT OF INTERESTS

The Authors declare that there is no conflict of interest.

REFERENCES

- Lazzerini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: Lessons from rheumatoid arthritis. *Eur Heart J*. 2017;38:1717–27.
- Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. *BMJ*. 2016;352:h6819.
- Parlindungan F, Hidayat R, Sumariyono S, Koesnoe S. Bone turnover imbalance in rheumatoid arthritis: Relationship between tumor necrosis factor- α and dickkopf-1 with bone turnover markers. *J Musculoskelet Res*. 2022;25.
- World Health Organization. Rheumatoid arthritis [Internet]. World Health Organization. 2023 [cited 2024 Mar 3]. Available from: <https://www.who.int/news-room/fact-sheets/detail/rheumatoid-arthritis>
- Black RJ, Cross M, Haile LM, et al. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2023;5:e594–610.
- Hidayat R, Suryana BPP, Wijaya LKW, et al. Diagnosis dan pengelolaan arthritis reumatoid. Jakarta: Indonesian Rheumatology Association; 2021.
- Suryana BPP, Hidayat R, Sarmidi S, et al. Characteristics and prevalence of clinical remission of rheumatoid arthritis in a nationwide study from Indonesia. *Int J Rheum Dis*. 2024;27.
- Pandit A, Londhey V, Chawla B, Khedkar U, Sundaram S, Asgaonkar DS. Complete heart block in a case of rheumatoid arthritis. *J Assoc Physicians India*. 2013;61:836–8.
- Ahern M, Lever J V, Cosh J. Complete heart block in rheumatoid arthritis. *Ann Rheum Dis*. 1983;42:389–97.
- Dihi B, Eljazouli H, Bouzerda A, Khatouri A. A complete atrioventricular block revealing rheumatoid arthritis: A case report. *SAS J Med*. 2022;8:430–2.
- Rezuş E, Macovei LA, Burlui AM, Cardoneanu A, Rezuş C. Ischemic heart disease and rheumatoid arthritis—two conditions, the same background. *Life*. 2021;11:1042.
- Villecco AS, De Liberali E, Bianchi FB, Pisi E, Di Patologia I. Antibodies to cardiac conducting tissue and abnormalities of cardiac conduction in rheumatoid arthritis. *Clin Exp Immunol*. 1983;53:536–40.
- Seferović PM, Ristić AD, Maksimović R, et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. *Rheumatology*. 2006;45:iv39–42.
- Rawla P. Cardiac and vascular complications in rheumatoid arthritis. *Reumatologia*. 2019;57:27–36.
- Plastiras SC, Moutsopoulos HM. Arrhythmias and conduction disturbances in autoimmune rheumatic disorders. *Arrhythm Electrophysiol Rev*. 2021;10:17–25.
- Sierra-Galan LM, Bhatia M, Alberto-Delgado AL, et al. Cardiac magnetic resonance in rheumatology to detect cardiac involvement since early and pre-clinical stages of the autoimmune diseases: A narrative review. *Front Cardiovasc Med*. 2022;9:870200.
- Ntusi NAB, Francis JM, Gumede F, et al. Cardiovascular magnetic resonance characterization of myocardial and vascular function in rheumatoid arthritis patients. *Hellenic J Cardiol*. 2019;60:28–35.
- Kishimoto T. IL-6 from laboratory to bedside. *Clin Rev Allergy Immunol*. 2005;28:177–86.
- Castell J V, Gómez-lechón MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: Regulation of acute-phase protein synthesis by interleukin-6. *Hepatology*. 1990;12:1179–86.
- Jego TG, Bataille RG, Pellat-Deceunynck C. Interleukin-6 is a growth factor for nonmalignant human plasmablasts. *Blood*. 2001;97:1817–22.
- Choy E, Ganeshalingam K, Semb AG, Szekanecz Z, Nurmohamed M. Cardiovascular risk in rheumatoid arthritis: Recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. *Rheumatology*. 2014;53:2143–54.
- Lazzerini PE, Acampa M, Cupelli M, et al. Unravelling atrioventricular block risk in inflammatory diseases: Systemic inflammation acutely delays atrioventricular conduction via a cytokine-mediated inhibition of connexin43 expression. *J Am Heart Assoc*. 2021;10:e022095.
- Baek HJ, Lim MJ, Park W, et al. Efficacy and safety of tocilizumab in Korean patients with active rheumatoid arthritis. *Korean J Intern Med*. 2019;34:917–31.
- Biggioggero M, Crotti C, Becciolini A, Favalli EG.

- Tocilizumab in the treatment of rheumatoid arthritis: An evidence-based review and patient selection. *Drug Des Devel Ther.* 2019;13:57–70.
25. Scott LJ. Tocilizumab: A review in rheumatoid arthritis. *Drugs.* 2017;77:1865–79.
 26. Chen DY, Chen YM, Hsieh TY, Hsieh CW, Lin CC, Lan JL. Significant effects of biologic therapy on lipid profiles and insulin resistance in patients with rheumatoid arthritis. *Arthritis Res Ther.* 2015;17.
 27. Rao VU, Pavlov A, Klearman M, et al. An evaluation of risk factors for major adverse cardiovascular events during tocilizumab therapy. *Arthritis Rheumatol.* 2015;67:372–80.
 28. Castagné B, Viprey M, Martin J, Schott AM, Cucherat M, Soubrier M. Cardiovascular safety of tocilizumab: A systematic review and network meta-analysis. *PLoS One.* 2019;14.
 29. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet.* 2008;371:987–97.
 30. Lazzerini PE, Acampa M, Capecchi PL, et al. Antiarrhythmic potential of anticytokine therapy in rheumatoid arthritis: Tocilizumab reduces corrected QT interval by controlling systemic inflammation. *Arthritis Care Res (Hoboken).* 2015;67:332–9.
 31. Khader Y, Beran A, Ghazaleh S, Lee-Smith W, Altork N. Predictors of remission in rheumatoid arthritis patients treated with biologics: a systematic review and meta-analysis. *Clin Rheumatol.* 2022;41:3615–27.
 32. Wang J, Devenport J, Low JM, Yu D, Hitraya E. Relationship between baseline and early changes in C-reactive protein and interleukin-6 levels and clinical response to Tocilizumab in rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2016;68:882–5.
 33. Hussain A, Tarahomi T, Singh L, Bollampally M, Heydari-Kamjani M, Kesselman MM. Cardiovascular risk associated with TNF alpha inhibitor use in patients with rheumatoid arthritis. *Cureus.* 2021;13:e17938.
 34. Sinagra E, Perricone G, Romano C, Cottone M. Heart failure and anti-tumor necrosis factor-alpha in systemic chronic inflammatory diseases. *Eur J Intern Med.* 2013;24:385–92.
 35. Anand CP, Al-Juburi A, Sandeep B. Heart block occurring during infliximab therapy: a report of two cases. *Am J Gastroenterol Suppl.* 2003;98:S144.
 36. Siebert S, Amos N, Lawson TM. Complete heart block after infliximab therapy. *Rheumatology.* 2008;47:228–9.
 37. Lee H, Lee S II, Kim HO. Recent advances in basic and clinical aspects of rheumatoid arthritis-associated interstitial lung diseases. *J Rheum Dis.* 2022;29:61–70.