Extensive triple vessel coronary artery disease in a young male with juvenile idiopathic arthritis

Nqoba Tsabedze 1,*, Mpoti Seboka 2, Dineo Mpanya 1 and Ahmed Solomon 2

1 Division of Cardiology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
2 Division of Rheumatology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

*Correspondence address: Division of Cardiology, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand and the Charlotte Maxeke Johannesburg Academic Hospital, 17 Jubilee Road, Parktown, 2193, Johannesburg, South Africa. Tel: + 27 11 488 3611, Fax: + 27 11 642 9041; E-mail: Nqoba.Tsabedze@wits.ac.za

Abstract

The risk of cardiovascular disease in patients with chronic inflammatory joint conditions is substantially increased compared to the general population. We present a case of a 27-year-old male with a chronic history of juvenile idiopathic arthritis (JIA) who presented with denovo acutely decompensated chronic heart failure. He had no traditional risk factors for atherosclerotic cardiovascular disease (ASCVD). However, during his workup for dilated cardiomyopathy, he was found to have extensive triple vessel disease on coronary artery angiography, and this was subsequently thought to be the most likely aetiology for the dilated cardiomyopathy despite being of young age. The chronic JIA was identified as the principal risk factor for the ischaemic cardiomyopathy. Clinicians treating patients with rheumatological conditions should routinely screen for ASCVD, despite the absence of traditional cardiovascular risk factors.

INTRODUCTION

The risk of cardiovascular disease (CVD) in patients with chronic inflammatory joint conditions is substantially increased when compared to the general population [1]. The underlying chronic inflammation may affect the cardiovascular system, resulting in accelerated atherosclerosis, myocarditis or pericarditis [2]. This case report emphasizes the importance of routine screening for atherosclerotic cardiovascular disease (ASCVD) in young patients with chronic inflammatory joint diseases.

CASE REPORT

We present a case of a 27-year-old male with a 1-month history of neck and lower back pain associated with worsening dyspnea on exertion. He had no prior history of angina, syncope, palpitations, flu-like illness, vomiting or diarrhoea. In addition, he had no family history of premature CVD or traditional ASCVD risk factors. Specifically, he reported no history of cigarette smoking or any form of substance abuse.

On clinical examination, he had conjunctival pallor, grade three pedal oedema and abdominal ascites. Examination of the cardiovascular system revealed an elevated jugular venous pressure, a myopathic displaced apex beat with a right parasternal heave and an S3 gallop. He was in New York Heart Association functional class III. His respiratory examination was normal.

The musculoskeletal examination revealed loss of cervical lordosis, tender and swollen joint count of eight, fixed flexion deformity of the elbows, ankylosis of the wrists and the proximal interphalangeal joints of both hands. The clinical disease activity index score was 34, signifying a high rheumatologic disease activity.

All inflammatory markers were elevated (Table 1), and the rheumatologic serological studies were unremarkable (Table 2). The Human immunodeficiency virus ELISA screen was negative. A resting electrocardiogram (ECG) showed a narrow QRS complex sinus tachycardia (Fig. 1). Echocardiography demonstrated four-chamber enlargement with global hypokinesis of the left ventricle and a left ventricular ejection fraction of 20–25% (Fig. 2). The diagnostic coronary angiogram revealed extensive triple vessel disease (Fig. 3), with a syntax score I of 36.5. Furthermore, computed tomography angiography of the neck and brain revealed large vessel vasculitis of the common carotid and middle cerebral arteries. The vasculitis flare was subsequently treated with two cycles of cyclophosphamide at 13 mg/kg, administered 2 weeks apart.

The patients’ rheumatic symptoms were treated with pulsed solumedrol 1 g for 3 days, followed by prednisone...
at 0.5 mg/kg. As part of the heart failure therapy, the patient was acutely initiated on furosemide, low dose carvedilol, an angiotensin-converting enzyme inhibitor and spironolactone, to which he responded well. The patient was also treated with simvastatin, baclofen, chloroquine, methotrexate, folic acid and carbamazepine. The ECG did not show any features suggestive of chloroquine-induced QT prolongation (QTc > 450 ms) as both the QT and corrected QT interval were 308 and 429 ms, respectively.

The differential diagnoses were ischaemic cardiomyopathy secondary to accelerated atherosclerosis and a vasculopathy of the coronary arteries as a sequela of the juvenile idiopathic arthritis (JIA). A differential diagnosis of cyclophosphamide-induced cardiomyopathy was also entertained.

The institutional heart team decided to refer the patient for elective coronary artery bypass graft surgery once the inflammatory markers had settled. Unfortunately, 3 weeks later, the patient experienced a sudden cardiac arrest while at home. The likely cause of death was a lethal arrhythmia such as ventricular tachycardia. An intracardiac defibrillator would have been an ideal therapy to prevent his sudden cardiac death. However, in our local clinical setting, such devices are not readily available due to their high cost.

**DISCUSSION**

JIA refers to a group of conditions characterized by inflammatory joint disease of unknown aetiology, occurring before the age of 16 years and lasting more than 6 weeks [3]. Patients with JIA have been found to have impaired endothelial dysfunction and elevated levels of pro-inflammatory cytokines, which play a significant role in the development of ASCVD [4, 5].

In our patient, cytokines and chemokines implicated in the pathogenesis of rheumatoid arthritis most likely led to prematurity accelerated atherosclerosis. Furthermore, chronic inflammatory joint pain may have led to physical inactivity, a well-established risk factor for ASCVD. As such, the increased inflammation, corticosteroid use and reduced physical activity may well have had a synergistic effect on advancing ASCVD [6]. Sonographic surrogate markers of early endothelial dysfunction such as carotid intima-media thickness, flow-mediated dilatation and pulse-wave velocity could have played a crucial role in diagnosing ASCVD early [7].

Although our patient did not report a history of flu-like symptoms on index presentation, a possible missed diagnosis of viral myocarditis was considered. Furthermore, a diagnosis of coronary artery disease superimposed on genetic dilated cardiomyopathy cannot be excluded with certainty. We did not screen first-degree relatives for dilated cardiomyopathy nor perform genetic analysis to identify a possible genetic cause for the heart failure [8]. Cardiomyopathy genetic tests are not readily available in state funded hospitals in South Africa.

Cyclophosphamide-induced cardiomyopathy was also considered as part of the differential diagnosis. However, our patient only received a low cyclophosphamide dose of 13 mg/kg per cycle, making this diagnosis unlikely. Cyclophosphamide-induced cardiotoxicity is dose-dependent, and the total dose of

| Table 1. Basic laboratory studies |
|----------------------------------|
| **Laboratory study** | **Value** | **Reference range** |
| Sodium | 138 | 136–145 mmol/L |
| Potassium | 4.3 | 3.5–5.1 mmol/L |
| Urea | 7.4 | 2.1–7.1 mmol/L |
| Creatinine | 77 | 64–104 μmol/L |
| Estimated glomerular filtration rate | 135.4 | >60 mL/min |
| Calcium | 2.25 | 2.15–2.50 mmol/L |
| Magnesium | 0.78 | 0.63–1.05 mmol/L |
| Liver Function Tests | | |
| Total protein | 83 | 60–78 g/L |
| Aspartate transaminase | 144 | 13–35 U/L |
| Alanine transaminase | 62 | 7–35 U/L |
| Alkaline phosphatase | 172 | 42–98 U/L |
| Gamma-glutamyl transferase | 142 | <40 U/L |
| Total bilirubin | 6 | 5–21 μmol/L |
| Albumin | 33 | 35–52 g/L |
| Lipid profile | | |
| Total cholesterol | 2.83 | <4.0 mmol/L |
| Triglyceride | 0.72 | <1.7 mmol/L |
| LDL cholesterol | 1.94 | <1.8 mmol/L |
| HDL cholesterol | 0.41 | >1.0 mmol/L |
| Full Blood Count | | |
| Haemoglobin | 9.3 | 11.6–16.4 g/dL |
| Platelets | 475 | 186–454 × 10^12/L |
| White blood cells | 8.42 | 3.9–12.60 × 10^9/L |
| Red blood cells | 4.16 | 3.93–5.40 × 10^12/L |
| Mean corpuscular volume | 76.2 | 78.9–98.5 fL |
| Cardiac enzymes | | |
| Creatine kinase | 31 | 20–180 U/L |
| CK-MB | 1.21 | 0.00–6.22 μg/L |
| Inflammatory Markers | | |
| Erythrocyte sedimentation rate | 120 | 0–10 mm/h |
| C-reactive protein | 132 | <10 mg/L |

CK-MB = creatine kinase-MB, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

| Table 2. Rheumatologic serologic studies and hypercoagulability studies |
|----------------------------------|
| **Laboratory study** | **Value** | **Reference range** |
| Anti-nuclear antibodies | Negative | |
| Anti-cyclic citrullinated peptide antibody | 2.0 | <20 U/mL |
| Thyroglobulin | 42.6 | 3.5–77.0 μg/L |
| Anti-thyroglobulin antibody | 12 | <115 U/mL |
| Anti-proteinase 3 antibody | 1.0 | 0–0.9 U/mL |
| Anti-myeloperoxidase antibody | 1.0 | 0–0.9 U/mL |
| Direct Coombs (typing) | | |
| IgG | positive | |
| C3d | negative | |
| Coagulation | | |
| INR | 1.29 | 2.0–3.0 |
| Prothrombin time | 18.2 | 14.0 s (control) |

Ig = immunoglobulin, INR = international normalized ratio.
cyclophosphamide therapy associated with cardiotoxicity is usually 150 mg/kg and above [9, 10].

In conclusion, we recommend optimal treatment of the primary rheumatological condition and active screening for ASCVD despite the absence of traditional cardiovascular risk factors. The clinical use of vascular biomarkers of early atherosclerosis may also be considered.
ACKNOWLEDGEMENTS
The authors would like to thank their colleagues in the Division of Cardiology, Charlotte Maxeke Johannesburg Academic Hospital for their assistance.

CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest.

FUNDING
The study was funded by Carnegie Corporation of New York Grant No. B 8749.RO1, Discovery Foundation, South African Medical Association and the South African Heart Association. The case report emanated from the research project titled ‘Genetics of idiopathic dilated cardiomyopathy in Johannesburg’.

ETHICAL APPROVAL
Approval to conduct the study was granted by the University of the Witwatersrand Human Research Ethics Committee (M150467).

CONSENT
Permission to publish the case report was obtained from the patients’ mother, as the patient had already demised.

GUARANTOR
Dr Nqoba Tsabedze.

REFERENCES
1. Solomon DH, Peters MJ, Nurmohamed MT, Dixon W. Unresolved questions in rheumatology: motion for debate: the data support evidence-based management recommendations for cardiovascular disease in rheumatoid arthritis. Arthritis Rheum 2013;65:1675–83. https://doi.org/10.1002/art.37975.
2. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;76:17–28. https://doi.org/10.1136/annrheumdis-2016-209775.
3. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
4. Vlahos AP, Theocharis P, Bechlioulis A, Naka KK, Vakalis K, Papamichael ND et al. Changes in vascular function and structure in juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:1736–44. https://doi.org/10.1002/art.20613.
5. Yilmaz M, Kendirli SG, Altintas D, Bingöl G, Antmen B. Cytokine levels in serum of patients with juvenile rheumatoid arthritis. Clin Rheumatol 2001;20:30–5. https://doi.org/10.1007/s100670170100.
6. Coulson EJ, Ng W-F, Goff I, Foster HE. Cardiovascular risk in juvenile idiopathic arthritis. Rheumatology 2013;52:1163–71. https://doi.org/10.1093/rheumatology/ket106.
7. Barsalou J, Bradley TJ, Silverman ED. Cardiovascular risk in pediatric-onset rheumatological diseases. Arthritis Res Ther 2013;15:212. https://doi.org/10.1186/ar4212.
8. Schultheiss HP, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE et al. Dilated cardiomyopathy. Nat Rev Dis Primers 2019;5:32. https://doi.org/10.1038/s41572-019-0084-1.
9. Goldberg MA, Antin JH, Guinan EC, Rappeport JM. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. Blood 1986;68:1114–8. https://doi.org/10.1182/blood.V68.5.1114.1114.
10. Pai V, Nahata M. Cardiotoxicity of chemotherapeutic agents. Incidence, treatment and prevention. Drug safety: an international journal of medical toxicology and drug experience. Drug Safety 2000;22:263–302. 0114-5916/00/0004-0263/$20.00/0.