Azathioprine-induced eosinophilic myocarditis in a patient with ANCA-associated vasculitis

Sirs,

Eosinophilic myocarditis (EM) is often drug-induced and managed with steroids and/or other immunosuppressive drugs after stopping the causative agent. We describe for the first time azathioprine as the most probable cause of EM.

We report the case of a 61-year old male who was recently diagnosed with systemic antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. After induction treatment with plasmapheresis, rituximab, cyclophosphamide and steroids, azathioprine was started as maintenance treatment. At that time the estimated glomerular filtration rate (eGFR by MDRD) was 48 ml/min/1.73m^2.

Two weeks after starting azathioprine the patient developed fever, chills, myalgia, headache and concentrated urine. Blood pressure was 100/60 mmHg, heart rate 110 bpm and temperature 38.5°C. Laboratory examinations showed a C-reactive protein (CRP) of 250 mg/l, eGFR of 29 ml/min/1.73m^2, mild leucocytosis and normal eosinophil counts. The urinary sediment demonstrated leukocytes, bacteria and erythrocytes. Initial management of suspected septic shock included broad-spectrum antibiotics and fluid resuscitation. After 24 hours, fever and hypotension persisted and the patient developed chest pain, increased central venous pressure and basal crackles upon pulmonary auscultation. The electrocardiogram showed non-specific repolarisation abnormalities and laboratory investigations showed an elevated troponin T of 3.32 µg/L (reference <0.05) and creatinine kinase of 239 U/L (reference <171). Transthoracic echocardiography (TTE) showed a reduced left ventricular ejection fraction (LVEF) of 27% (normal >60%) and global hypokinesia, altogether consistent with a diagnosis of myocarditis. Azathioprine was stopped and dobutamine initiated to optimise the haemodynamic situation and renal function. Microbiological analyses were negative for bacterial, viral and parasitic infections. The patient recovered swiftly: eGFR was restored to 43 ml/min/1.73m^2, troponin T decreased and TTE showed an improved LVEF of 59% (Fig. 1). Low dose azathioprine 25 mg bd was restarted.

One week later, the patient again developed fever, chest pain and dyspnea, accompanied by hypotension (RR 93/63 mmHg), a decline in eGFR to 30 ml/min/1.73m^2 and an increase in troponin T (0.211 µg/L). TTE showed global hypokinesia and a decline in LVEF (34%). Cardiac magnetic resonance imaging (MRI) confirmed the impaired LVEF and global hypokinesia. Furthermore, midwall delayed enhancement of the septum was seen, characteristic of myocarditis. Subsequent coronary angiography was unremarkable. Myocardial biopsies were taken to further differentiate between infectious, ANCA-associated or eosinophilic myocarditis. Of note, ANCA-titers were decreasing since diagnosis. Accordingly, it seems unlikely that the EM is related to the underlying systemic vasculitis. Histopathological evaluation confirmed myocarditis with abundant macrophages and eosinophils, fitting EM. Again, azathioprine was stopped and the patient recovered quickly: eGFR returned to 54 ml/min/1.73m^2 and LVEF normalised (66%). The patient was started on mycophenolate mofetil.

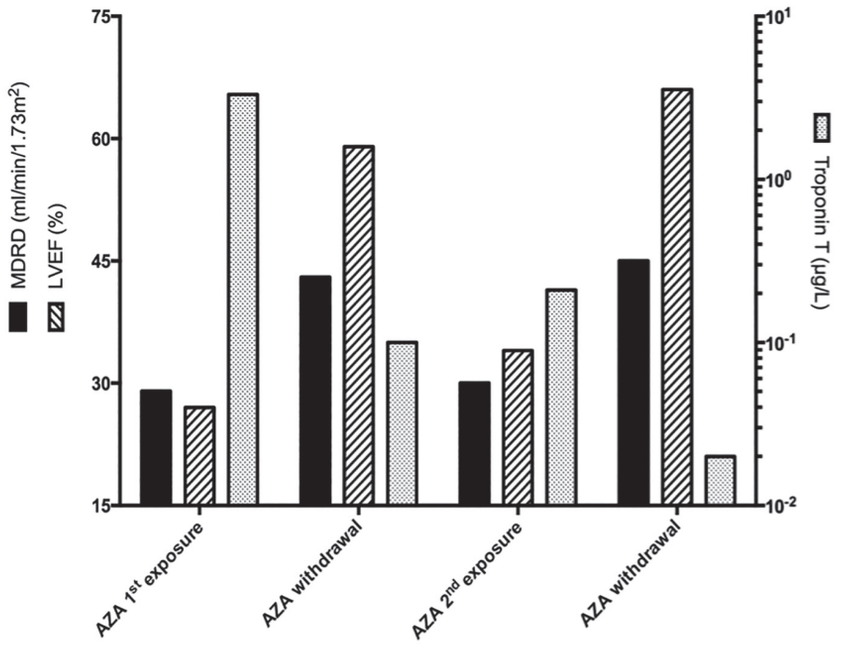

Fig. 1. Chronological overview of events showing the fluctuation of renal function as depicted by eGFR (MDRD, ml/min/1.73m^2), myocardial function as depicted by left ventricular ejection fraction (LVEF %) and serum levels of troponin T (µg/L) in relation to azathioprine introduction and withdrawal.

Here, we describe for the first time a patient with histopathologically proven EM most probably caused by azathioprine. Using the Naranjo causality scale (1), azathioprine classifies as 'definite' causative agent (score 10/13).

Drug-related myocarditis is considered the most common cause of EM. The incidence of EM is unknown and it is probably underdiagnosed, often being first discovered on autopsy. Diagnostic delay can lead to irreversible myocardial injury. Well-known drugs associated with EM are antibiotics, diuretics and the antipsychotic agent clozapine (2-4). Cardiac imaging such as MRI can be useful to detect EM, (5, 6) however endomyocardial biopsy remains the gold standard (2, 7). EM can be successfully treated with immunosuppression including azathioprine (4, 8). The latter emphasises the relevance of reporting EM as a newly identified side-effect related to azathioprine.

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