Rituximab reversed cardiac involvement of Wegener’s granulomatosis: magnetic resonance imaging assessment

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Clinical case

Summary

Introduction > Cardiac involvement is a rare manifestation of Wegener granulomatosis (WG). Because its prognosis can be poor, it must be diagnosed early to be treated adequately. We report the disease course of a patient who received rituximab to treat cardiac involvement documented by contrast-enhanced cardiac magnetic resonance imaging (ceCMR).

Observation > This WG patient developed myocarditis with atrioventricular block. CeCMR proved useful in the diagnosis and follow-up of cardiac involvement. Several unsuccessful regimens preceded the prescription of rituximab. Two months later, regression of the myocarditis shown by ceCMR images was correlated with electrophysiological improvement.

Discussion > CeCMR assessment of a heart conduction defect in a patient with WG showed that this tool was useful for the diagnosis and follow-up of cardiac involvement in this vasculitis. Rituximab was an effective treatment in this patient.

Résumé

Efficacité du rituximab pour le traitement de l’atteinte cardiaque de la maladie de Wegener, évaluation par imagerie par résonance magnétique

Introduction > L’atteinte cardiaque est rare au cours de la maladie de Wegener. Le pronostic de cette atteinte est réservé et nécessite un diagnostic précoc pour permettre un traitement approprié. Nous rapportons l’évolution d’un patient atteint de maladie de Wegener traité par rituximab dans le cadre d’une atteinte cardiaque documentée par imagerie par résonance magnétique.

Case > Nous rapportons un cas de maladie de Wegener compliqué de myocardite avec bloc auriculoventriculaire. L’imagerie cardiaque par résonance magnétique s’est révélée utile pour le diagnostic et le suivi de l’atteinte myocardique de la vascularite. Notre patient avait reçu de nombreux traitements qui n’avaient pas permis de maintenir de rémission prolongée. Un traitement par rituximab a permis d’obtenir une régression de l’atteinte myocardique, attestée par les données de l’imagerie cardiaque par résonance magnétique et l’étude électrophysiologique.

Discussion > L’imagerie cardiaque par résonance magnétique apparaît être un outil intéressant pour l’évaluation diagnostique et le suivi des atteintes cardiaques de la maladie de Wegener. Le traitement par rituximab s’est révélé efficace chez ce patient.
Cardiac involvement is a relatively rare manifestation of Wegener granulomatosis (WG), affecting 4 to 25% [1–3] of patients with this disorder. Because its prognosis can be poor, it must be diagnosed early to be treated adequately. We report here the case of a patient successfully treated with rituximab for cardiac involvement. Both the diagnosis and success of treatment were documented by contrast-enhanced cardiac magnetic resonance imaging (ceCMR).

Case report

In 1991, a 33-year-old man was diagnosed with pansinusitis, pulmonary nodules, hematuria and proteinuria. Antineutrophil cytoplasmic antibodies (ANCA) in a diffuse cytoplasmic pattern were detected by immunofluorescence, and anti-proteinase 3 specificity by ELISA (enzyme-linked immunosorbent assay). Nasal biopsy further confirmed the diagnosis of WG by showing fibrinoid necrotizing vasculitis with granulomatous inflammation. The patient received 18 infusions of cyclophosphamide combined with oral prednisone. A relapse in April 1995 was characterized by, among other signs, pericarditis and atrial flutter. Renewed treatment with cyclophosphamide pulses and oral prednisone led to a return to sinus rhythm, but persistent first-degree atrioventricular block remained. Cyclophosphamide treatment was permanently stopped in June 1997 because the patient developed hemorrhagic cystitis. A second relapse occurred three months later, characterized echocardiographically by right ventricular enlargement, pulmonary arterial hypertension, and pericardial thickening. Transesophageal echocardiography showed nodules in the interatrial septum. The patient received a daily methylprednisolone pulse for 3 consecutive days (15 mg/kg), followed by oral prednisone (1 mg/kg/d) combined with intravenous immunoglobulin infusions every 3 weeks. The pulmonary arterial hypertension and interatrial septum nodules disappeared. In December 1997, pyoderma gangrenosum appeared. Azathioprine replaced the intravenous immunoglobulin, and prednisone was continued. Pulmonary nodules appeared in January 1999. Mycophenolate mofetil (2 g/d then 3 g/d) was administered, in combination with prednisone and immunosuppressants. Rituximab had previously been given to WG patients as salvage therapy after cyclophosphamide failure, with promising results were reported in some cases [4].

Cardiac imaging was performed in August 2005 because of persistent conduction disorders. Echocardiography was normal. CeCMR showed multiple midwall intramyocardial foci with increased intramyocardial signal intensities on both early and late gadolinium-DOTA-enhanced sequences, especially in the septal and lateral walls (figure 1A and 1B). These findings were highly suggestive of acute inflammation. The early enhancement did not affect the subendocardium and did not match any of the coronary artery territory, thereby ruling out a diagnosis of ischemic infarction. The late enhancement was attributed to acute myocardial necrosis associated with inflammation.

In December 2005, pyoderma gangrenosum and lung nodules reappeared. ANCA were still negative, but the B-cell count had risen to 11%. PR interval was 280 ms. A 24-h Holter-ECG showed a sinus rhythm and a 3.6-second period of high-grade atrioventricular block (figure 2B). Methotrexate and mycophenolate mofetil were continued, rituximab was reintroduced (4 weekly infusions of 375 mg/m²). Skin ulcers healed after 1 week. Eight weeks after the first rituximab infusion, the B-cell count dropped to 0%, the ECG PR interval was shortened to 220 ms, and the left anterior bundle branch hemiblock disappeared (figure 2C). The 24-hour Holter ECG was normal. A new ceCMR (figure 1C) showed regression of intramyocardial signal intensities on both the T2-weighted and early gadolinium-DOTA-enhanced images, and late enhancement images were suggestive of myocardial scar tissue. At that time, the size of the lung nodules had not changed significantly.

Discussion

This case report describes a patient with a long-standing history of WG, characterized by ENT and pulmonary manifestations, pyoderma gangrenosum and cardiac involvement. Because conventional regimens failed to control his disease, rituximab was administered, in combination with prednisone and immunosuppressants. Rituximab had previously been given to WG patients as salvage therapy after cyclophosphamide failure, and promising results were reported in some cases [4].

Cardiac involvement in WG patients has been described previously [1] but is usually considered to be rare. Walton [5] reported 11% of patients with cardiac involvement had...
granulomata and 28% focal necrotizing arteriolitis of the heart. A retrospective study of 27 patients with cardiac involvement reported the following histopathological findings [6]: 50% coronary arteritis (medium-sized vessels) or heart tissue involvement (small vessel necrotizing vasculitis and granulomata within the tissue); 50% pericarditis; 25% myocarditis; 21% valvulitis/endocarditis; 17% conduction system granulomata; 13% sinus node arteritis; 13% atrioventricular node arteritis; and, finally, 8% epicarditis. Conduction defects of all degrees have been described, from intraventricular conduction defects to first- and second-degree atrioventricular blocks and complete heart block. These conduction defects can, however, regress with treatment [5–11].

A retrospective study of 85 patients who underwent systematic echocardiography [12] found abnormalities in 73 (86%), and these were directly related to WG in 26 (36%). Thirteen of the latter (50%) had left ventricular systolic dysfunction with a reduced ejection fraction, and 5 (19%) had pericardial effusion. Valve regurgitation (54% mitral, 38% tricuspid, and 23% aortic) and left ventricular hypertrophy (38%) were also frequent. Although myocarditis can be suspected based on ECG, echocardiography is usually insufficient to confirm or characterize myocardial involvement. Transesophageal echocardiography in our patient initially showed intramyocardial nodules, a feature rarely been described in WG [11,13]. At the time of the last flare, transthoracic echocardiography was considered normal, but ceCMR imaging revealed inflammatory involvement of the myocardium. After the second rituximab cycle, we observed
impressive regression of abnormalities on ceCMR and substantial ECG improvement. This suggests that ceCMR may be more sensitive than transthoracic echocardiography for evaluating WG-related cardiac involvement. It also appears to be a reliable tool for monitoring therapeutic efficacy.

CeCMR provides important contributions to the diagnosis and serial assessment of patients with coronary artery disease, cardiomyopathy, and myocarditis from causes other than vasculitis [14]. Enhancement may be seen on late gadolinium-DOTA-enhanced inversion recovery prepared gradient echo acquisitions; it is thought to correspond to the absence of viable myocytes, which leads to an enlarged volume of gadolinium distribution, due to either its passive diffusion across ruptured myocyte membranes into the intracellular space (acute necrosis) or expanded interstitial space (collagenous scarring), as described in ischemic coronary artery disease. In contrast to myocardial ischemia, in patients with vasculitis, the distribution of the late enhanced cardiac lesions does not correspond to any particular epicardial coronary artery territory and is often mid-wall instead of subendocardial or transmural. Conversely, for now, ceCMR can reveal areas of cardiac inflammation, but is unlikely to distinguish reliably between vasculitic or granulomatous lesions.

Studies by Keogh et al. [15] and Eriksson [16] have pointed out that clinical response to rituximab may be associated with effective B-lymphocyte depletion. All clinical relapses reported after rituximab treatment were preceded by reconstitution of the B-lymphocyte population, 6 to 12 months after the last rituximab cycle. The circulating CD19 or CD20-positive B-lymphocyte count was not systematically and serially measured and was not used as an indicator for determining the need for reinfusion in our patient, who was among the first WG patients we treated with rituximab [17]. We did, however, observe similar variations in the B-cell count, which rose at the time of relapses and rapidly decreased after rituximab courses. This observation demonstrates, that ceCMR can contribute to the diagnosis of myocardial lesions in WG and their repeated assessment during therapy, and that rituximab can be effective against these specific cardiac manifestations of WG.

Conflicts of interest: none

References