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Article type: Clinical image

Received: November 18, 2020.

Accepted: December 14, 2020.

Published online: December 30, 2020.

ISSN: 1897-9483

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Title:
Cardiac involvement as a fatal complication of granulomatosis with polyangiitis

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Short title: Fatal cardiac complication of granulomatosis with polyangiitis

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Conflict of interest: none declared.
Granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis with granuloma formation and is associated with antineutrophil cytoplasmatic antibodies (cANCA) with specificity against proteinase-3 (PRG3) [1]. As opposed to the upper respiratory tract (92%), lungs (85%) and kidneys (77%), cardiac involvement is a rare manifestation of GPA (3-44%) [1–2]. Pericarditis is the most common heart lesion (50%) in the GPA population with cardiac involvement, followed by myocarditis (25%), valvular involvement (21%), conduction block (17%) and myocardial infarction (11%). Heart lesions in GPA are likely to be underdiagnosed [3].

A previously healthy 41-year-old man was admitted to a district hospital due to sudden hearing deterioration, arthralgia with joint stiffness, feet paresthesia and petechiae on the skin of the lower limbs. Urine test revealed proteinuria (2g/24h) and erythrocyturia. Peripheral blood eosinophil count was normal (0.27G/l). Mucosal changes in sphenoid sinus together with ground-glass changes and nodules in the lungs were noted in computed tomography. After starting the treatment by 3 pulses of methylprednisolone (1 500mg), the patient was transferred to our department.

On admission, his general condition was good, cANCA titer was 1:320, and PRG3 antibodies were 55.08 RU/ml. Pauci-immune glomerulonephritis with crescents was diagnosed in a histopathological examination. Birmingham Vasculitis Activity Score for GPA (BVAS/WG) was 9 points. As a remission induction, 5 monthly pulses of cyclophosphamide (CYC) (3 064mg/m² in total) and prednisone (0.8mg/kg) were administered with good clinical response.

During admission to our daily department on schedule for the 6th pulse of CYC, surprisingly the patient complained about the significant deterioration of effort tolerance, dyspnea class II according to New York Hear Association, elevated heart rate at rest (110–120/min.), as well
as lower limbs edemas. Blood tests showed increased concentration of creatinine to 1.7 mg/dl (0.7 – 1.3 mg/dl), brain natriuretic peptide 3 353 pg/ml (< 73 pg/ml) and high sensitive troponin I 0.055 ng/ml (< 0.03 ng/ml), creatine kinase myocardial band level was at normal range. Electrocardiogram (ECG) documented sinus tachycardia.

In echocardiography (ECHO) left ventricular ejection fraction was 40%, severe aortic and moderate mitral regurgitation, hypokinesia of inferior heart wall with diffuse segmental dysfunction of cardiac muscle contractility were also detected (Figure 1 panel A). During immediate hospitalization in the Cardiology Department, there were no signs of infective endocarditis in transesophageal ECHO, and blood cultures were negative. Coronarography did not show signs of coronary artery disease. Tissue characterization techniques in magnetic resonance imaging (MRI) revealed subtle diffuse active myocarditis most likely associated with GPA (Figure 1 panel B, C).

Due to the high disease activity (BVAS/WG 12 points), 7 therapeutic plasma exchanges were performed followed by 3 weekly infusions of rituximab (375 mg/m²), which caused partial improvement of the patient’s general condition.

Despite the treatment, the patient suddenly died at home in anticipation of a fourth pulse of rituximab and valves replacement.

We present the case to emphasize the need for heart monitoring (ECG and ECHO) in the entire GPA population. However, MRI is the most accurate non-invasive technique to diagnose cardiac lesions in GPA patients[4]. The probable cause of the patient’s death was arrhythmia e.g. atrioventricular complete heart block, which was reported by Colin GC et al. [5]. Pacemaker implantation might have prevented fatal complication of GPA in our case. Moreover, immediate aortic valve replacement should also have been taken into
consideration. Guidelines for the detection and management of heart involvement in GPA are lacking, and further research is required.

Bibliography:


Figure 1 panel A

Long axis systolic and long axis diastolic still frames from routine balanced steady state free precession cine sequence showing slight left atrial and marked left ventricular enlargement (left ventricular end-diastolic volume index of 169 ml/m²), with severe aortic insufficiency (reg. volume in a phase-contrast sequence: 65ml/cycle). Left ventricular ejection fraction was moderately reduced at 45%.

(Siemens Aera 1.5T, Erlangen, Germany).
Figure 1 panel B

Late gadolinium enhancement. Minimal, subendocardial/intramural late gadolinium enhancement in mid-infero-septal and inferior segments. Images acquired with a phase-sensitive inversion recovery sequence.

(Siemens Aera, 1.5T Erlangen, Germany).
Figure 1 panel C

Parametric mapping of the basal short axis slice showing inhomogenous myocardium with local areas of increased native T1 relaxation time (left: local native T1 increases)
up to 1110 ms; ref. range: 993+/-21ms [951-1035ms]; images acquired with a modified Look-Locker inversion recovery sequence) and locally increased signal in the T2 weighted short tau inversion recovery pointing to patchy edema (centre; mid-ventricular slice), matching the areas of locally elevated T2 time predominantly in the septum and infero-lateral segments (right: local increases up to 54 ms; ref. range: 44+/-2,4ms [39-49 ms]; images acquired with a balanced steady-state free precession sequence). This is suggestive of inhomogenous diffuse acute injury due to myocardial involvement. Small pericardial effusion is apparent in all three images.

(Siemens Aera, 1,5T Erlangen, Germany).