

Pemphigus-associated cardiomyopathy: report of autoimmune myocarditis and review of literature

Andrea Frustaci^{1*}, Marco Francone², Romina Verardo³, Rossella Scialla³, Giulia Bagnato³, Maria Alfarano¹, Cristina Chimenti¹, Emanuela Frustaci³, Luigi Sansone⁴ and Matteo Russo⁵

¹Department of Clinical, Internal, Anesthesiologist and Cardiovascular Sciences, Sapienza University, Viale del Policlinico 155, Rome, 00161, Italy; ²Department of Radiological, Oncological and Pathological Sciences, Sapienza University, Rome, Italy; ³Cellular and Molecular Cardiology Lab, IRCCS L. Spallanzani, Rome, Italy; ⁴Laboratory of Molecular and Cellular Pathology, IRCCS San Raffaele Pisana, Rome, Italy; and ⁵MEBIC Consortium, San Raffaele Open University and IRCCS San Raffaele Pisana, Rome, Italy

Abstract

Pemphigus is a rare disease characterized by bullous lesions of the skin and mucous membranes. The aetiology is autoimmune and related to the formation of IgG autoantibodies against desmogleins, which are structural proteins of desmosomes that ensure the stability of contacts between cells. Cardiac involvement in patients with pemphigus is poorly documented. We report the data in the literature on this topic and a case of pemphigus-associated autoimmune myocarditis with damage of intercalated disc responding to immunosuppressive therapy. The occurrence of cardiomyopathy with left ventricular dysfunction in patients affected by pemphigus should be appropriately screened with endomyocardial biopsy as it could be the myocardial extension of a potentially reversible autoimmune disorder.

Keywords Pemphigus; Autoimmune myocarditis; Cardiomyopathy

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*Correspondence to: Prof. Andrea Frustaci, Department of Clinical, Internal, Anesthesiologist and Cardiovascular Sciences, Sapienza University, Viale del Policlinico 155, 00161, Rome, Italy. Tel: + 39 06 5517 0520. Email: biocard@inmi.it

Introduction

Pemphigus is a rare disease characterized by bullous lesions of the skin and mucous membranes. In Central Europe, the annual incidence is two cases per million inhabitants.¹ The aetiology is autoimmune and related to the formation of IgG autoantibodies against desmogleins, which are structural proteins of desmosomes belonging to the cadherin family that provide stable intercellular bonds. The binding of these autoantibodies to desmogleins alters the structural integrity of the desmosome and consequently the mechanical stability of the epidermis and mucous membranes, causing detachment of the cells through acantholysis and the formation of bubbles, vesicles, and erosions.² Similarly to most autoimmune disorders, the pathogenesis of pemphigus is likely to be linked to a complex interaction between environmental factors, genetic predisposition, and characteristics of the immune system. There are three major clinical forms of pemphigus: vulgaris, foliaceus, and paraneoplastic.

Pemphigus vulgaris, responsible of 70% of cases, represents the most severe form with prevalent clinical onset between 40 and 60 years and very painful ulcerative lesions of the skin and mucous membranes.² Pemphigus foliaceus can be sporadic or endemic and equally affects men and women. Endemic areas are Brazil, Colombia, and Perù. Skin lesions are erythematous and crusted blisters spread over the scalp, the face, and the trunk, sometimes painful. Mucosal involvement is rare.

Pemphigus has been associated to autoimmune disorders such as vasculitis and type 1 diabetes mellitus and haematological, oropharyngeal, gastrointestinal, and lung neoplasias.³

The disease is characterized by the production of IgG autoantibodies against desmogleins, in particular desmogleins 1 and 3, which are membrane proteins of the desmosome promoting extracellular binding to adjacent cells. The autoantibodies produced against these proteins cause the detachment of keratinocytes in the epidermis resulting in the formation of blisters and erosions. In patients with

pemphigus, not only the skin but also other organs may be involved. Indeed, systemic involvement including renal and cardiovascular disease occurs in about one-third of patients with the foliaceus variant of pemphigus.⁴

Therefore, a molecular mimicry mechanism can be hypothesized that determines the interaction of autoantibodies against other tissues including cardiomyocytes.

The identification of an associated cardiomyopathy in patients with pemphigus is poorly documented and investigated in terms of pathogenesis. We report the data in the literature on this topic and identification by endomyocardial biopsy of a case of autoimmune myocarditis responding to immunosuppressive therapy.

Cardiac involvement in patients with pemphigus

Cardiac involvement in pemphigus is limited in the literature to few and often single case studies, although the third cause of death in pemphigus patients is cardiovascular after pneumonia and septicemia.⁵

Abreu-Velez *et al.*⁶ described the presence of cardiac autoantibodies in patients affected by a new form of endemic pemphigus foliaceus found in El-Bagre, Colombia, South America, with high incidence of sudden cardiac death, occurring in about 14% of cases before than 50 years.^{7,8} Patients with the variant 'El-Bagre' of endemic pemphigus foliaceus share several autoantigens with patients affected with paraneoplastic pemphigus.⁹ The authors tested the presence of cardiac autoantibodies in serum of 15 patients with the variant 'El-Bagre' of endemic pemphigus foliaceus and 15 controls utilizing human heart samples from autopsies of affected patients and beef, mouse, and rat heart samples. They described the presence of cardiac autoantibodies in 46% of patients with the variant 'El-Bagre' of endemic pemphigus foliaceus. The autoantibodies were polyclonal and reactive against numerous desmosome adhesion proteins (such as desmoplakins I and II and connexin 43) and co-localized in blood vessels, sarcomeric fibres, and Purkinje system. No lymphocytic infiltration in the autopsy human heart of patients affected by the variant 'El-Bagre' of endemic pemphigus foliaceus was detected. However, the fibrolipomatous substitution of 15% of the myocardium of the right ventricle was observed. The authors conclude that sudden death in these patients could be related to the presence of autoantibodies against the heart conduction system and desmosomes. Moreover, some patients with the variant 'El-Bagre' of endemic pemphigus foliaceus have autoantibodies against the 'bullous pemphigoid antigen 1' that is a plakine; it has been documented that mutation of the 'bullous pemphigoid antigen 1' induces skin weakness and neuromuscular deterioration in mice skin.^{10,11} So it can be postulated that

autoantibodies in these patients can react against the cardiac conduction system.

In another issue, Abreu-Velez *et al.*¹² reported cardiac rhythm abnormalities in 30 patients with the variant 'El-Bagre' of endemic pemphigus foliaceus compared with 30 controls. Heart rhythm abnormalities were more frequent in these patients, including sinus bradycardia, left bundle branch block, left anterior branch block, and left posterior branch block. Moreover, the authors tested the serum of the patient population and controls for cardiac autoantibodies and found in the patients with the variant 'El-Bagre' of endemic pemphigus foliaceus cardiac autoantibodies reactive against adherence junctions of nodal cells and His bundle in cow heart samples. Therefore, the authors hypothesized that autoantibodies in patients with this form of pemphigus may be polyclonal and reactive against the heart conduction tissue. In their commentary editorial, Lee and Melduni¹³ underline some interesting aspects of the study of Abreu-Velez and colleagues,¹² although the sample size is quite small and a definite causative correlation between autoimmunity and cardiac arrhythmias is lacking. First, the variant 'El-Bagre' of endemic pemphigus foliaceus is limited to the State of Colombia, and this suggests a possible interaction between genes and the environment. Second, the presence of polyclonal autoantibodies against structural desmosomal proteins against the heart could be related to the development of cardiomyopathy and electrical instability.

In a further report, Abreu-Velez *et al.*¹⁴ demonstrated that patients with the variant 'El-Bagre' of endemic pemphigus foliaceus have polyclonal autoantibodies reactive against the areae compositae that are a special type of cardiac intercellular junctions with the role of stabilizing the intercellular junctions in the heart. Patients with reactive autoantibodies against the areae compositae also showed ventricular hypertrophy at echocardiography; therefore, the authors hypothesized that the rupture of these junctions, due to an autoimmune process, may be implicated in the development of myocardial hypertrophy as a compensatory mechanism.

Finally, a report of autoimmune myocarditis has been obtained in a single case,¹⁵ where the final diagnosis of myocarditis was supposed and not confirmed by an endomyocardial biopsy.

Immunosuppression is the cornerstone of the treatment of pemphigus. The association between steroids and immunosuppressive drugs is useful to limit side effects of steroids. In fact, steroid pulse therapy may be associated with cardiac dysfunction as suggested by the reduction of global longitudinal strain by speckle-tracking 2D echocardiography and QT dispersion on the surface electrocardiogram.¹⁶

Immune-mediated mechanisms are associated with cardiovascular disorders.¹⁷ Herein, we report the manifestation of progressive cardiac dilatation and dysfunction, which

pathologic substrate is characterized by an autoimmune myocarditis and damage of intercalated disc responding to immunosuppressive therapy.

Case report

A 31-year-old man, who was previously in good health, was hospitalized for acute heart failure associated to oral (*Figure 1A*) and genital ulcerative lesions and blisters of trunk, abdomen, and limb skin (*Figure 1B*) appeared 3 weeks earlier. He appeared in New York Heart Association (NYHA) functional class III, symptomatic for dyspnoea due to mild exertion and with peripheral oedema. Routine laboratory exams were within limits except white blood cells (12.160/UL, 75% neutrophils), C-reactive protein (30 mg/mL, nv 0–0.5 mg/dL), high-sensitive cardiac troponin (0.5 mcg/L, nv < 0.014 mcg/L), and N-terminal pro-B-type natriuretic peptide (458.7 pg/mL, nv 0–254 pg/mL). The evaluation of oral and genital ulcers was negative for autoimmune and viral aetiology. HLA-B51, screened to investigate Behcet's disease, was negative while patient serology revealed an elevated antibody titre for desmoglein 3.

A skin perilesional biopsy showed sub-epidermal vesicles with associate infiltrate of lymphocytes, histiocytes, and eosinophils. Direct immunofluorescence of perilesional skin showed infiltration of IgG autoantibodies against desmoglein 3 and C3d along the basement membrane of keratinocytes, suggesting the diagnosis of pemphigus vulgaris.

On cardiac side, electrocardiogram showed sinus rhythm (85 b.p.m.) with diffuse and non-specific ventricular repolarization abnormalities. Two-dimensional echocardiography showed a dilated and globally hypokinetic left ventricle (LV) [LV end-diastolic diameter = 62 mm, LV end-diastolic volume = 132 mL/m², LV ejection fraction (LVEF) calculated with biplane Simpson method = 24%], moderate mitral regurgitation, and left atrial enlargement. Right ventricle showed mild dilation with preserved systolic function and mild tricuspid regurgitation. No pericardial effusion was present.

Cardiac magnetic resonance (CMR) confirmed a severe LV dilation (end-diastolic volume/body surface area 153.8 mL/m², *Figure 1C*, with reduced LVEF of 22%, *Figure 1D* and Supporting Information, *Movie S1*). No myocardial oedema on T2-weighted images was detected. Late gadolinium enhancement technique revealed only a nuanced area of non-specific fibrotic meaning in the inferior junctional site and in the sub-epicardial area at the level of the interventricular septum.

Invasive studies including coronary and LV angiography and endomyocardial biopsy were performed. Coronary arteries were normal. Left endomyocardial biopsy revealed the presence of lymphomononuclear infiltrates with associated necrosis of adjacent cardiomyocytes, suggesting an active

myocarditis (*Figure 1G*). The inflammatory infiltrates were positive for CD45RO+ T lymphocytes. Cardiomyocyte overexpression of TLR-4 and the absence of viral genomes on myocardial tissue (as PCR for the most common cardiotropic viruses was negative) was indicative of an immune-mediated myocarditis. Assessment of anti-heart antibodies obtained on frozen section from normal myocardium of 0 group showed an intense (*Figure 1K*) positivity extended to the intercalated disc. At electron microscopy, damage of intercalated disc was revealed, suggesting a correlation with pemphigus (*Figure 1I*).

Patient was treated with prednisone 1 mg/kg/day for 4 weeks followed by 0.33 mg/kg/day for 5 months and azathioprine 2 mg/kg/day for 6 months according to the TIMIC protocol.¹⁹ At 2 months of follow-up, the patient presented a remarkable clinical improvement; the NYHA functional class from III became I. The electrocardiogram showed sinus rhythm (70 b.p.m.) with no specific ventricular repolarization abnormalities nor QT prolongation. At 2D echocardiography, the LV appeared of reduced size (LV end-diastolic diameter = 54 mm) with recovered function. Also, the left atrium returned to normal size, and the mitral regurgitation became mild with no haemodynamic effects. CMR confirmed the recovery of cardiac dimensions (*Figure 1E*) with LV function rising to 45% EF (*Figure 1F* and Supporting Information, *Movie S2*). The small nuanced area of non-specific fibrotic meaning in the inferior junctional site and in the sub-epicardial area at the level of the interventricular septum was unchanged.

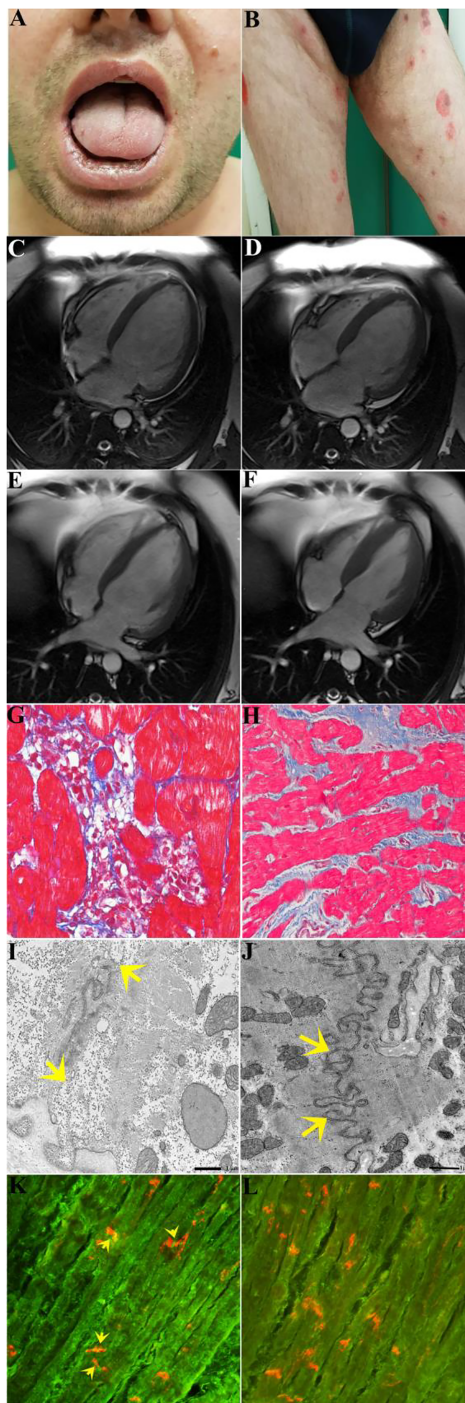
Cardiac improvement was maintained at a 6 month follow-up CMR. At that time, control endomyocardial biopsy revealed resolution of myocardial inflammation (*Figure 1H*) as well as recovery of intercalated disc (*Figure 1J* and *1L*).

Discussion

Although pemphigus has been associated with various autoimmune disorders as well as haematological, oropharyngeal, gastrointestinal, and lung neoplasias,³ cardiac involvement in pemphigus has been rarely documented.^{6–15}

In the case of pemphigus, the most likely explanation is an antigenic mimicry between cardiomyocytes and the basement membrane zone. For example, collagen XVII, which is an antigen of bullous pemphigus, has been shown to be expressed in mouse heart.¹⁸ Furthermore, collagen XVII has also been reported to be the target of IgA autoantibodies, in a case of IgA-type bullous dermatosis arising after heart transplantation.^{19,20} However, beyond the registration of increased cardiac dimension and reduced contractility sometimes associated with pemphigus, cause and mechanisms of cardiac damage have not been clarified so far. On the other hand, definition of histological and molecular pathway is

Figure 1 Clinical–histologic findings of pemphigus vulgaris-associated autoimmune myocarditis before and after immunosuppression therapy. (A and B) Oral and skin lesions caused by pemphigus vulgaris. (C–F) Cardiac magnetic resonance images showing cardiac dilatation [end-diastolic volume/body surface area (BSA) and end-systolic volume/BSA: 154 and 119 mL/m², respectively] and dysfunction (left ventricular ejection fraction: 22%), which recovers at 2 months of follow-up (end-diastolic volume/BSA and end-systolic volume/BSA: 95.18 and 52.65 mL/m², respectively) with left ventricular ejection fraction of 45% following immunosuppressive therapy. (G and H) Left ventricular endomyocardial biopsy before (G) and after immunosuppression (H) showing active lymphocytic myocarditis progressing to healed phase. (I) Detail of a disorganized intercalated disc. Between the arrows, residual junctional complexes are still visible. The bar represents 1 μm. (J) After therapy, the recovery of the intercalated disc is evident, with all types of junctions well recovered in all regions of the disc. The bar represents 1 μm. (K) Shows positive anti-heart autoantibodies on human heart extended to intercalated disc (in red co-localization with antibody anti-n-cadherin, yellow arrow) (400×). (L) Shows negative serum for anti-heart autoantibodies on human heart and on intercalated disc (400×).



essential for the instauration of a specific and effective treatment.

In our report, a pemphigus-associated progressive cardiac dilatation and dysfunction has been investigated by LV endomyocardial biopsy and its histologic substrate attributed to an autoimmune myocarditis. Autoimmune nature of myocardial inflammation was based on negative PCR for viral genomes, presence of anti-heart autoantibodies, and overexpression of TLR4 on mycardiocytes. Pathogenetic correlation of myocarditis to pemphigus was supported by serologic elevation of antibody titre for desmoglein 3 and by the reversible damage of intercalated disc at electron microscopy.

Immunosuppressive therapy based on combination of steroids with azathioprine as from TIMIC trial²¹ was able to revert the cardiac disease with the LVEF rising from 22% to 45% and NYHA class from III to I. The patient had no side effects from therapy; no QT prolongation was detected on the electrocardiogram.

The association between steroid and immunosuppressive drugs is useful to limit the possible cardiac side effects of high-dose steroid therapy alone.^{16,22}

It has been demonstrated that the activation of Foxo transcription factor and subsequent overexpression of atrogin-1 promotes ubiquitin-dependent proteasome proteolysis of endogenous contractile elements causing cardiac dysfunction.²³

Presence of myocardial inflammation was not suspected from CMR findings as no specific alteration of T1, T2, and late gadolinium enhancement signals was registered. This is not unusual for cardiomyopathic phenotype of myocarditis where CMR sensitivity for inflammation is around 50%²⁴ and explained with a slowly progressive disorder.

Contribution of endomyocardial biopsy was crucial as it could demonstrate the presence of autoimmune myocarditis

and connect the myocardial to the skin lesion revealing the common damage of intercalated disc.

In conclusion, occurrence of dilated cardiomyopathy in patients with pemphigus should be appropriately screened with CMR and possibly endomyocardial biopsy as it could be the myocardial extension of a potentially reversible autoimmune disorder.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Movie S1. Cardiac dilatation with severe left ventricular dysfunction (EF 22%) (Movie S1) that recover after immunosuppressive therapy (EF 45%) (Movie S2).

Movie S2. Cardiac dilatation with severe left ventricular dysfunction (EF 22%) (Movie S1) that recover after immunosuppressive therapy (EF 45%) (Movie S2).

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