



Peripartum cardiomyopathy, an autoimmune manifestation of allograft rejection?

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ABSTRACT

The timing of peripartum cardiomyopathy (PPCM) in association with pregnancy is typical of autoimmune conditions. This review addresses this fact by presenting PPCM as an organ specific autoimmune response (though not necessarily as an outright autoimmune condition), akin to autoimmune responses seen with complications of allogeneic organ transplantations. Since pregnancy represents a semi-allograft (representing paternal alloantigens), pregnancy and allogeneic organ transplants can be expected to be subject to similar allograft tolerance mechanisms, and also to share potential complications of normal allograft tolerance. This review suggests that PPCM represents a cardio-toxic autoimmune component within a more general immunological malfunction of tolerance of the fetal allograft by the maternal immune system. Treatment of PPCM with therapies, proven successful in graft versus host disease and organ rejection, may, therefore, be successful. Their success would also be confirmatory of such a concept.

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1. Introduction

Noted in the 18th century, pregnancy associated heart failure was first described in 1937 [1]. In the early 70s, at Chicago's Cook County Hospital, it was defined as peripartum cardiomyopathy (PPCM), characterized by cardiac decompen-

sation in the last month of pregnancy or up to five months postpartum [2]. This definition has not much changed [3,4], though PPCM is now believed also to occur earlier in pregnancy [5]. With "unknown" etiology, PPCM's current definition still includes absence of obviously determinable causes [3,4].

Diagnoses are still frequently delayed and/or overlooked, as symptoms may mimic normal physiologic findings of pregnancy or be mistaken for preeclampsia/eclampsia [3]. Both conditions may present with congestive heart failure and/or pulmonary edema, but preeclampsia/eclampsia, in

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contrast to PPCM, is usually not characterized by left ventricular systolic dysfunction [6].

2. Etiology and pathophysiology

PPCM is amongst only a small number of conditions, characterized by first occurrence and recurrence in association with pregnancy. Amongst those, where an etiology is known, all are considered autoimmune conditions, and this kind of occurrence pattern has, therefore, been characterized as autoimmune [7]. It, therefore, does not surprise that PPCM has been suggested to represent an autoimmune disease [8–11].

We, however, in subtle contrast, consider PPCM one (amongst many possible) organ specific autoimmune expressions of a defect in normal allograft tolerance during pregnancy. Like better understood xenotransplantation failures, resulting in graft-versus-host disease (GVHD) or outright transplant rejection, the fetal–placental allograft of pregnancy can at times also be expected to fail [12,13]. In analogy to failure in organ transplant tolerance, failure in fetal–placental tolerance will result in immunological responses of the maternal immune system, which can be autoimmune in nature, reflective of a more general mechanism of GVHD or rejection.

Immunological tolerance of allografts, at least to a degree, appears dependent on bi-directional cell traffic between donor organ (in pregnancy, the fetal–placental unit) and recipient host (in pregnancy, the mother) and resultant microchimerisms [12–14]. We recently described how well known complications of pregnancy (i.e., selected miscarriages, preeclampsia/eclampsia and dermatoses of pregnancy) mimic classical features of acute GVHD [13], and, therefore, may represent immunologic malfunctions of normal fetal tolerance mechanisms in pregnancy. Pregnancy associated hypertensive conditions (like preeclampsia/eclampsia) are, of course, statistically highly associated with PPCM [2–5].

One expects malfunctions in (maternal) tolerance especially with unusual histocompatibility (HLA) antigens challenges. In pregnancy this happens with implantation, when the maternal immune system for the first time sees significant amounts of paternal HLA, and peripartum, when during delivery cell traffic peaks. If allograft tolerance is meant to fail, it should happen at such peak antigen exposure periods, a finding supported by conditions of so-called hyperplacentosis (i.e., large placental mass), which uniformly present with increased risk towards failure of allograft tolerance (i.e., preeclampsia/eclampsia) [12,13].

The most frequent conditions of significant hyperplacentosis is probably multiple births, and twin pregnancies are not only associated with increased preeclampsia/eclampsia risk [12] but also with a significantly increased risk towards PPCM [3–5].

That the maternal immune system, stimulated by paternal HLA and under appropriate genetic preconditions, can give rise to autoimmune responses, was first reported in women with rheumatoid arthritis [15]. In turn, autoimmune responses after implantation have been associated with increased miscarriage (i.e., allograft rejection) risk, and peripartum autoimmune responses may occur with preeclampsia/eclampsia and, of course, with autoimmune disease flares [12–14]. Organ specific (i.e., thyroid) [16] and non-organ specific (i.e., systemic lupus erythematosus) [17] exacerbate

primarily peri- and postpartum, when fetal-maternal cell traffic peaks.

That the heart can be subject to organ, and even tissue-specific immune responses is well established. Platzbecker et al. reported a case of acute heart failure with dramatic decrease in left ventricular function after allogeneic blood stem cell transplantation in a patient with GVHD grade III [18]. The heart was found massively infiltrated by donor CD8-positive lymphocytes, with extensive damage to the heart muscle. Warraich et al. reported myosin autoantibodies during acute rejection after heart transplantation, concluding that IgG3 and IgM antibodies may influence the frequency and severity of allograft rejection [19]. Higher anti-myosin IgG antibodies were also reported in patients with poorer cardiac transplantation outcomes and during acute rejection [20] and Ferry et al reported higher anti-endothelial antibodies with chronic rejection [21].

3. Autoimmunity in non-pregnancy associated cardiomyopathy

Outside of pregnancy, chronic myocarditis [22,23] and especially idiopathic dilated cardiomyopathy [24–29] have been associated with anti-cardiac autoimmune responses. As in cardiac transplantation, autoantibodies appear polyclonal, associated with cytokine abnormalities [27,28] and can be organ-specific or not [29]. Some heart-specific autoantibodies are poorly defined [24], but most are anti-myosin antibodies [25,26] and some exert functional effects on cardiac myocytes in vitro and in vivo [29].

Reduction in autoantibody load via extracorporeal immunoadsorption improves ventricular function and cardiac symptoms [29], and pentoxifylline, a generally immunomodulatory agent, not only improves left ventricular ejection fraction concomitantly with reducing TNF-alpha levels in idiopathic cardiomyopathy [30], but also in PPCM [31].

Correlations between degree of (auto)immune abnormalities and cardiac function parameters further support an autoimmune etiology: Warraich et al. reported that plasma interferon gamma and the IgG3 fraction of anti-myosin antibodies prognostically correlated in patients with dilated cardiomyopathy [26]. Tatli and Kurum reported that treatment with carvedilol concomitantly improves symptoms, left ventricular function and suppresses inflammatory cytokines [28]. Antimyosin antibodies seem to correlate with left ventricular systolic function in chronic myocarditis [22].

4. PPCM's other characteristics of autoimmune conditions

Abnormal autoimmunity is familial and one autoimmune condition in an individual predisposes to the development of others [32]. Whether this applies to PPCM is unknown. PPCM, however, demonstrate a dramatically higher prevalence in African than Caucasians women [3,4], suggesting a genetic component to risk, and in this sense behaves like an autoimmune condition.

After pregnancy, autoimmune diseases may go into remission, only to clinically resurface later. In contrast, autoimmune phenomena, associated with GVHD, will be gone for ever, once an allograft has been removed. Removal of an organ transplant interrupts GVHD, just as removal of the fetal-

placental allograft by delivery or curettage interrupts preeclampsia/eclampsia [12,13]. It is, therefore, noteworthy that PPCM mostly improves spontaneously and clinically ultimately subsides [3,4]. In this sense, PPCM, therefore, once more behaves like a typical GVHD-associated autoimmune condition [13].

On occasion, PPCM-like symptoms of cardiac decompensation can, even in the absence of pregnancy, spontaneously reoccur [33]. The condition then behaves more like classical autoimmune diseases, which can flare any time and one may speculate that temporary microchimerism of pregnancy under such circumstances has become permanent [12–14], which has been suggested as cause of persistent autoimmunity [14].

Abnormal autoimmune function is frequently associated with hypercoagulable states and/or thrombophilias. The most common such association is the so-called anticardiolipin antibody syndrome, where the presence of antiphospholipid antibodies (APAs) greatly predisposes towards arterial and venous thrombotic events [34]. In full analogy, PPCM also seems highly associated with arterial and venous thromboses [3,33] though APAs, and other non-specific autoantibodies have so far not been investigated in this condition.

5. What speaks against it and why it matter?

Recent reports, implying that the hormone prolactin mediates PPCM [35], and that inhibition of prolactin may enhance recovery from PPCM [36] have been suggested to be contradictory to an autoimmune etiology for the condition. Such an opinion, however, ignores that elevated prolactin levels have been associated with abnormal autoimmune function in general [37,38], specific autoimmune conditions, such as systemic lupus erythematosus, rheumatoid arthritis and thyroid disease and that reduction of prolactin levels has been suggested as a promising treatment strategy [39]. Preliminary reports on the benefit of bromocriptin therapy in attempts to reduce prolactin levels in PPCM should, therefore, actually be seen as further support for an autoimmune etiology.

In most cases, standard cardiac interventions bridge a transitional period of impairment and allow the heart, based on the natural history of PPCM, to spontaneously recover. A minority will, however, never fully recover and some will even succumb [3–5]. Whether full recovery of the heart, indeed, occurs has recently been questioned when Lampert et al. demonstrated that, even in patients with apparently full clinical recovery, the cardiac muscle still demonstrates impaired responses to pharmacologically stress with dobutamine [40]. At the etiology directed treatments of PPCM should interrupt disease processes earlier and more efficiently and, therefore, hopefully lead to lower morbidity, mortality and permanent cardiac damage.

That manipulation of the immune system may be effective is supported by previously noted prolactin data and by preliminary experiences with intravenous immunoglobulin, which in inflammatory cardiomyopathy improved left ventricular function and decreased cytokine levels [23]. Intravenous immunoglobulin, of course, is a frequently used treatment in autoimmune diseases and GVHD-associated autoimmune abnormalities [13].

Other immuno-pharmacological interventions with carvedilol [28], pentoxifylline (30 and extracorporeal immunoabsorption [29] in non-pregnancy related autoimmune cardiac conditions are also supportive of such an experimental therapeutic approach towards PPCM. Modifying Koch's postulates, an autoimmune etiology for PPCM, within a GVHD-like pregnancy tolerance defect, would be strongly supported if immunological treatments, shown effective in tolerance complications during xenotransplantation, were to demonstrate similar effectiveness with PPCM, by successfully reducing morbidity, mortality and long-term cardiac effects. Since most PPCM cases are diagnosed after delivery, fetal effects of experimental therapies could initially be avoided by testing them only after delivery. PPCM is serious enough a condition to warrant such trials.

Take-home messages

- There is convincing circumstantial evidence in support of abnormal autoimmune function as an underlying pathophysiological mechanism in the development of PPCM.
- It is, however, tempting to speculate further that these observed autoimmune responses are not representative of an autoimmune condition, but reflect the typically observed autoimmune components of malfunctions in allograft (in this case pregnancy-) tolerance.
- Building on this concept, pharmaceutical interventions, which have been proven beneficial in organ transplant complications, may also represent effective therapy of at times life-threatening PPCM.

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Association of autoimmunity to peptidyl arginine deiminase type 4 with genotype and disease severity in rheumatoid arthritis

Protein citrullination is an important posttranslational modification recognized by rheumatoid arthritis (RA)-specific autoantibodies. One of the citrullinating enzymes, peptidyl arginine deiminase type 4 (PAD-4), is genetically associated with development of RA in some populations, although the mechanism(s) mediating this effect are not yet clear. There have been descriptions of anti-PAD-4 autoantibodies in different rheumatic diseases. This study was undertaken, **Harris ML et al. (Arthritis Rheum 2008; 58: 1958-67)** to investigate whether anti-PAD-4 antibodies are specific to RA, are associated with disease phenotype or severity, and whether PAD-4 polymorphisms influence the anti-PAD-4 autoantibody response. Sera from patients with established RA, patients with other rheumatic diseases, and healthy adults were assayed for anti-PAD-4 autoantibodies by immuno-precipitation of in vitro-translated PAD-4. The epitope(s) recognized by PAD-4 genotyping was performed on RA patients with the TagMan assay. Joint erosions were scored from hand and foot radiographs using the Sharp/van der Heijde method. PAD-4 autoantibodies were found in 36–42% of RA patients, and were very infrequent in controls. Recognition by anti-PAD-4 autoantibodies required the 119 N-terminal amino acids, which encompass the 3 non-synonymous polymorphisms associated with disease susceptibility. Strikingly, the anti-PAD-4 immune response was associated with the RA susceptibility haplotype of PADI4. Anti-PAD-4 antibodies were associated with more severe joint destruction in RA. These findings indicate that anti-PAD-4 antibodies are specific markers of RA, independently associated with more severe disease, suggesting that an anti-PAD-4 immune response may be involved in pathways of joint damage in this disease. Polymorphisms in the PADI4 gene influence the immune response to the PAD-4 protein, potentially contributing to disease propagation.